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Relationships Between Pancreatic Blood Flow and Secretion in the Dog

TOHRU TAKESHIMA, M.D., JIRO MIYAMOTO, M.D., YOJI IWASAKI, M.D., AND DAVID A. DREILING, M.D.*

Abstract

Relationships between pancreatic blood flow and secretion were studied in the dog following administrations of secretin, pancreozymin, and glucagon. In the experiments, a double thermistor, tissue blood flow meter was used for the measurement of the pancreatic blood flow.

The conclusions were: 1) the injection of secretin or PZ resulted in increases of both the pancreatic blood flow and secretion, as estimated by three parameters, that is, secretory rate, bicarbonate output and amylase output, corresponding to the dose amount of secretin or PZ; 2) a close correlation was found between the pancreatic blood flow and all of the pancreatic three parameters, that is, the pancreatic blood flow proved to be influenced not only by the secretory rate or bicarbonate output but also by the enzyme output.

Introduction

Studies of the dynamics of pancreatic blood flow are considered essential for elucidating the pathophysiology of pancreatic diseases. Although it has been previously shown that the pancreatic blood flow affects the pancreatic secretion, the reported results have been contradictory.

This investigation determined the effects of the exogenous hormones such as secretin, pancreozymin, and glucagon on canine pancreatic blood flow and secretion using a double thermistor blood flow meter.

Forty-two mongrel dogs, weighing 12–18 kg, fasted for more than 18 hours, were anesthesized with pentobarbital sodium (25 mg/kg) and then subjected to the operative procedure. Figure 1 shows the experimental protocol in which isotonic saline is continuously infused at a rate of 60 ml/hr into the femoral vein. The blood flow was measured by means of Hagihara (1) double-thermistor, tissue blood flow meter. The blood flow wire elements were connected to straight needles which were positioned in the parenchyma of the head of the pancreas.

The percent ratio of the blood flow change was obtained from the drop in flow taken as 100 percent when cardiac arrest is induced by rapid intravenous injection of 10 mEq of KCl. The pancreatic juice was collected via a drop-counter, through a polyvinyl tube inserted into the main pancreatic duct extraduodenally. Arterial blood pressure induced in the femoral catheter, the pancreatic blood flow changes and the drops of pancreatic juice were simultaneously recorded on an electric amplified system. Pancreatic juice collected every five minutes, was measured for volume, bicarbonate concentration (PH titration method) (2), and amylase concentration (Caraway method).

Results

The Effect of Secretin on the Pancreatic Blood Flow and Secretion

Figure 2 shows an individual experiment using an intravenous injection of 2 u/kg and 4 u/kg of secretion (Boots). With 2 u/kg of secretin, the pancreatic blood flow reached a peak value about one minute after the injection. Subsequently, the blood flow decreased gradually and returned to the control levels after 15–20 minutes. The secretory rate reached the peak later than the peak of the blood flow and then decreased gradually concomitant to the decrease of blood flow. The duration of increasing secretion was longer than that of increased blood flow.

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Requests for reprints should be sent to Tohru Takeshima, M.D., Dept. of Surgery, Institute of Clinical Medicine, Tsukuba University, Ibaraki, 305 Japan.

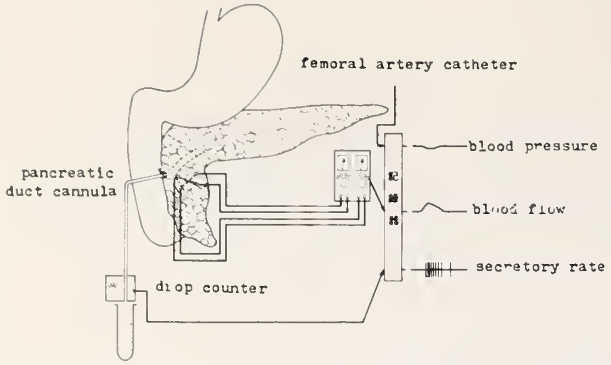

FIG. 1. The schema of the protocol used to study the effects of pancreatic hormones on pancreatic blood flow and exocrine secretion.

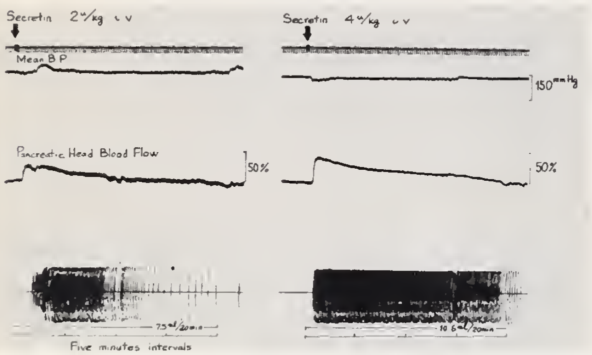

FIG. 2. An individual experiment showing the effects of IV secretin on pancreatic blood flow and secretory rate. Note that increase in pancreatic blood flow preceded augmentation of the secretory rate.

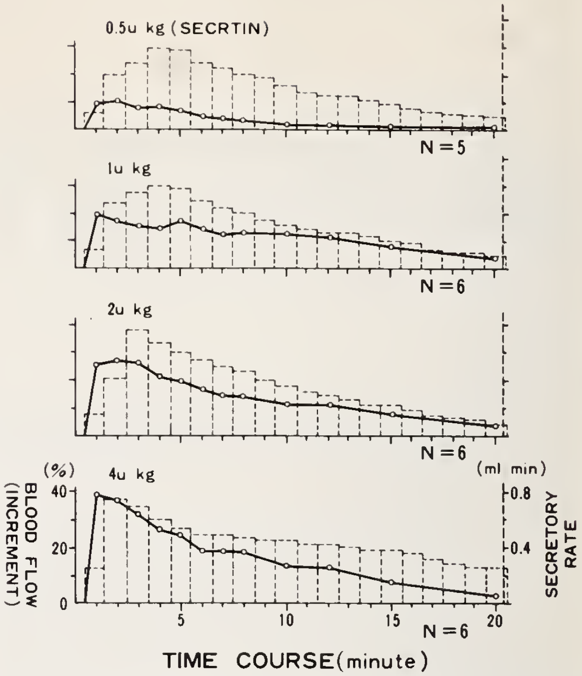

FIG. 3. Pancreatic flow and secretory data following IV secretin injections (0.5–4.0 u/kg) superimposed on continuous infusion of secretion (1 u/kg/hr). ○: percent increment of blood flow, □: secretory rate.

Figure 3 shows the change in rates of blood flow and secretory rate during the intravenous injection of 0.5, 1, 2 and 4 u/kg of secretin respectively under the continuous submaximal stimulation of 1 u/kg/hr of secretin. For a single injection of 2 u/kg of secretin, the increment of the pancreatic blood flow reached the peak value of 27.5 ± 7.4 (M ± SD) percent after two minutes, the peak of the secretory rate was observed after three minutes in 0.76 ± 0.30 (M ± SD) ml/min. As shown in Fig. 3, as the dose of secretin was increased, the peak and the duration time of the increased blood flow were augmented and the secretory rate increased. In most experiments, blood pressure decreased only following an injection of 4 u/kg of secretin.

Figure 4 illustrates the variation of the blood flow (an area generated by the blood flow curve), the secretory rate, the bicarbonate and amylase output per five minutes. Corresponding to the peak of the blood flow, each of the secretory parameters showed peaks in the first fraction and then decreased gradually in the succeeding ones. Using the values shown in Fig. 4 in determining the relation between the blood flow and the three factors, linear correlations were found between the increase rate of blood flow and those characterizing secretion (Fig. 5).

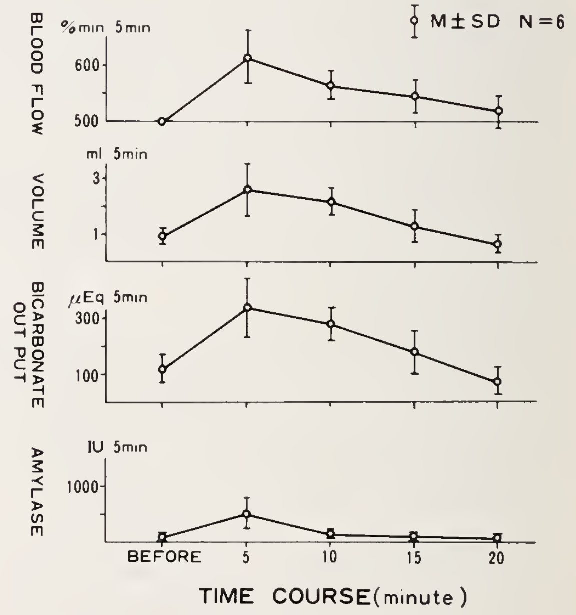

FIG. 4. Effects of secretin on pancreatic secretory rate, bicarbonate and amylase output following the stimulation by secretin (1 u/kg/hr). Note that the changes in blood flow correspond closely to exocrine pancreatic secretion.

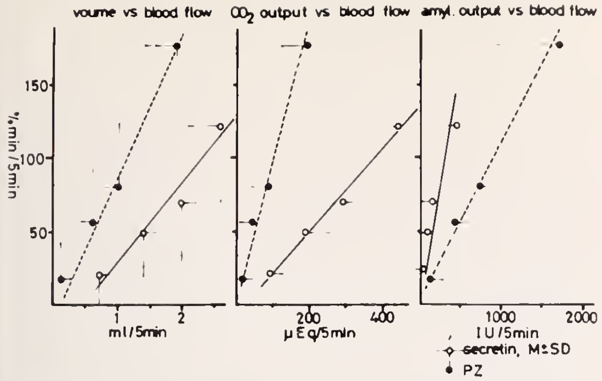

FIG. 5. Graphed data indicating a linear correlation between blood flow (vertical directions) changes and secretory rate, bicarbonate output, and amylase output.

The Effect of Pancreozymin (PZ) on the Pancreatic Blood Flow and the Secretion

Figure 6 shows the dose response curve of the blood flow change following intravenous injection of 0.5, 1, 2 and 4 u/kg of PZ superimposed on continuous infusion of 1 u/kg/hr secretin. The patterns of blood flow change were similar to those of secretin. However, the peak values were higher than those of corresponding secretin dosage and the duration of effect was shorter. The peak blood flow following the injection of 2 u/kg of PZ was 39.0 ± 33.9 (M ± SD) percent. Together with the pancreatic head blood flow, the pancreatic tail blood flow was simultaneously recorded. There was no marked differences in the pattern of blood flow between these two regions.

Figure 7 shows blood flow, secretory rate, the bicarbonate and amylase output for the PZ bolus as previously shown for the secretin injection. The increased blood flow in the first five minutes fraction after the PZ injection, was 175% min/5 min. This value is considerably greater than 119% min/5 min for the secretion injection. Yet the increases in secretory rate and bicarbonate output 1.7 ml/5 min and 210 μEq/5 min respectively following the PZ injection, were considerably smaller than 2.6 ml/5 min and 339 μEq/5 min respectively which were observed after secretin injection. The increment of amylase output was 3075 Iu/5 min for the PZ injection compared to 500 Iu/5 min for secretin. For PZ as for secretin, changes in blood flow paralleled exocrine secretion.

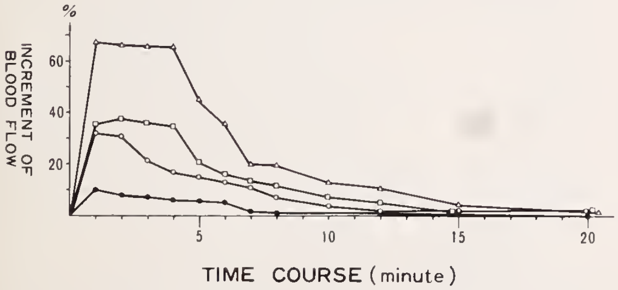

FIG. 6. Changes in the pancreatic blood flow after 0.5–4.0 u/kg of IV pancreozymin superimposed on continuous IV secretin infusion (1 u/kg/hr). ○: 0.5 u/kg of PZ, ●: 1 u/kg, □: 2 u/kg, △: 4 u/kg.

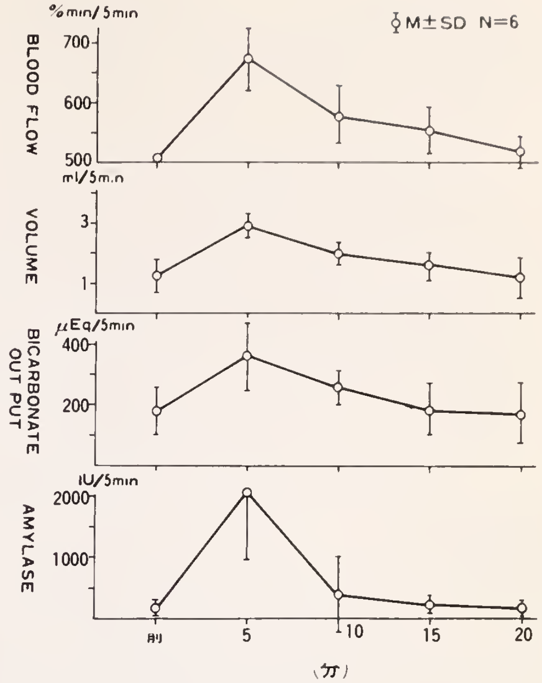

FIG. 7. Effects of PZ on pancreatic blood flow, secretory rate bicarbonate output, and amylase output. Note that the changes in blood flow vary synchronously with pancreatic exocrine secretion.

The Effect of Glucagon on Pancreatic Blood Flow and Secretion

Figure 8 graphs blood flow and pancreatic secretion after the intravenous injection of 1 mg of glucagon superimposed on continuous stimulation with 1 u/kg/h of secretin intravenously (IV). Following glucagon injection, all parameters decreased. In the fifteenth minute's fraction, the maximum inhibitions of 0.7 ml/5 ml for the secretory rate, 113 μEq/5 min for the bicarbonate output and 535 Iu/5 min for the amylase output were observed. At this time, the blood flow decrement was 60% min/5 min. The inhibitory change of the blood flow paralleled the decline of pancreatic secretion.

Discussion

Although there have been many reports concerning the relationship between pancreatic blood

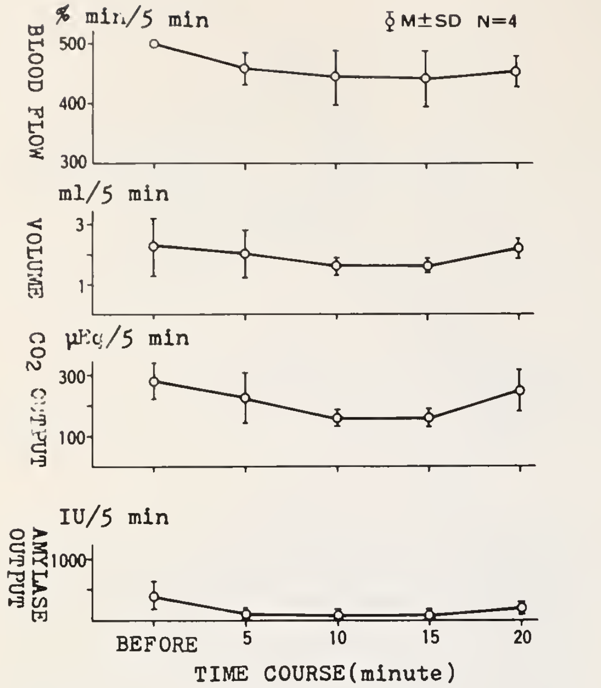

Fig. 8. Effects of glucagon superimposed upon continuous IV secretin (1 u/kg/hr.) on pancreatic blood flow secretory rate, bicarbonate output, and amylase output following stimulation by secretin (1 u/kg/hr). Note that the inhibitory changes in blood flow are closely related to the inhibition of pancreatic secretion.

flow and secretion of fluid and electrolyte, very few studies have compared blood flow with pancreatic enzyme output. This paper attempts to elucidate the relationship of pancreatic blood flow to the pancreatic secretion.

The Blood Flow Meter

The double thermistor tissue blood flow meter used for the experiments was initially developed by Gibbs (3), calculated blood flow upon the basis of heat loss from a tissue as measured by change in local temperature. Later, Hensel et al (4) and Hagihara et al (1) improved the apparatus. The change of blood flow in an area 3 mm in diameter is measured in the capillary bed by thermoelectric effect. Grayson (5) used this concept of heat conductivity to measure liver blood flow. The advantages of the double thermistor technique are the simplicity of apparatus, the absence of local tissue injury and the possibility for continuous recording. The absence of trauma is important in the pancreas because of its rich blood supply.

Effects of Secretin and PZ on Pancreatic Blood Flow and Secretion

Previous communications have suggested that secretin increases pancreatic blood flow. The experiments using the photo-cell method (6), thermostromuhr (7), electromagnetic flowmeter (8, 9), hydrogen clearance blood flow meter (10), clearance methods with radioisotopic such as ^{133}Xe (11) Rb (12), though different in technique, have all yielded data indicating IV secretin increases pancreatic blood flow. The present studies confirm this effect but in addition indicate a parallelism between flow, fluid electrolyte, and enzyme secretion.

After the PZ injection, the present experimental results reveal a more marked increase than after secretin. Some investigators have reported that PZ does not change pancreatic blood flow (13). Dorigotti (16) has found the increase in blood flow following PZ to be less than after secretin. Barlow (14) and Papp (15), on the other hand, reported that IV PZ produced a greater increase in blood flow than secretin. All investigators agree that the duration of effect on blood flow is shorter than the effect on pancreatic secretion. Babkin et al (17) have concluded from their data that minor changes in blood flow did not affect pancreatic secretion.

In the present experiment, blood flow changes were instantaneously recorded electronically. The change of secretory rate, however, was observed as changes in drops at the tip-end of the intubated catheter. Thus, it can be assumed that there is a time lag generated by the catheter dead space. The data of the present studies, nonetheless, indicate that pancreatic secretion does change concordantly with pancreatic blood flow.

Effects of Glucagon on Pancreatic Blood Flow and Secretion

In the present experiments, glucagon inhibition of blood flow and secretion was confirmed. The findings are in accord with the literature (18, 20). Schapiro (21) has suggested that these effects of glucagon were due to: 1) the decrease in the pancreatic blood flow, 2) the inhibition of gastric secretion, 3) the decrease in serum Ca due to cacitonin secretion, 4) the inhibition of endogenous secretin, 5) the hyperglycemia, and 6) the degranulating action on pancreatic acinar cells. Although the studies (22–24) all report post glucagon diminution of pancreatic blood flow, it is questionable as to whether the magnitude of blood flow inhibition, per se, is sufficient to account for the marked suppression of pancreatic secretion observed. Is the blood flow cause or effect? However, regardless of whether the blood flow change is a cause or result of the secretion change, of particular interest is the observation that following glucagon injection, the pancreatic secretion and blood flow show parallel depression.

Correlation Between Pancreatic Blood Flow and Secretion

Thus far, the data have indicated a close relationship between pancreatic blood flow and stimulants to pancreatic electrolyte secretion (secretin) to pancreatic enzyme production (PZ), as well as to inhibitors of both (glucagon). The question arises as to cause and effect, that is, whether the blood flow change depends on hormones injected or the alteration in pancreatic secretion. The bar graph in Fig. 9 clearly denies an absolute linear correlation between flow and secretion. For example, the increased blood flow generated by secretin is 255% min/20 min, compared to an increased secretory volume of 7.0 ml/20 min; for PZ the blood flow augmentation is 330% min/20/min (greater than secretin) compared to an increase in pancreatic flow of 3.0 ml/20 min (less than secretin). On the other hand, the amylase secretion increase following secretin, 796 Iu/20 min, is remarkably less than that observed for PZ, 2290 Iu/20 min. Analyzing the data from a strictly mathematical point of view one can construct the following equation relating blood flow to pancreatic secretion: $(\%\Delta BF) = a(\%\Delta PF) + b(\%\Delta AS)$ in which BF is blood flow, PF is pancreatic flow and AS is amylase secretion. This straight line holds true for the secretin and PZ stimulation data and yields the following values for the constants a and b—for a 25, for b 0.1. Using the equation and these constants, the percentage changes in pancreatic blood flow following glucagon were calculated from the observed percentage alterations in pancreatic flow and amylase secretion. The calculated data of pancreatic blood flow exactly matched the observed data. These findings strongly suggest that the alterations in secretion observed in these experiments were indeed related to the alterations flow.

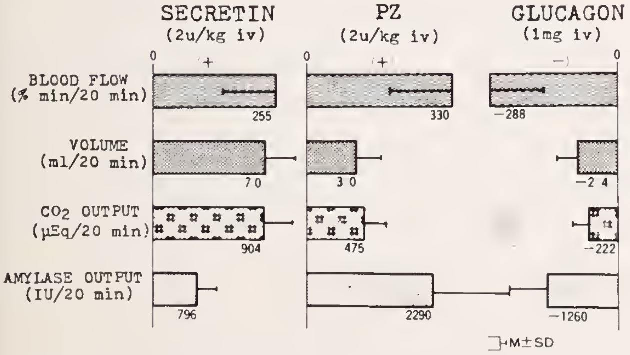

FIG. 9. Correlations between pancreatic blood flow and exocrine pancreatic secretion. Yet this correlation is not directly proportional for the secretory parameters. Note that the blood flow correlates not only with secretory rate and bicarbonate output, but also with amylase output.

Etiology of Pancreatic Blood Flow

Although the physiologic basis of alteration in pancreatic flow following the hormones is not understood; the following hypotheses have been offered: 1) the change is caused by alteration of metabolic demand (22), 2) the blood flow change is a direct action of the hormone itself and independent from the pancreatic secretory effect (25), 3) the hemodynamic effect is caused by the rise of the pancreatic duct pressure (26), 4) due to impurified substance contained in exogenous pancreatic hormones (27), and 5) finally the result of production of kinin substance such as kallikrein (25). However, other studies present data that appear to contradict these hypotheses (7, 12, 15, 28−30). More convincing are increasing experimental findings that augmentation of pancreatic blood flow may be a consequence of stimulated secretion. The mechanism would be increased metabolic demand and mediated through the release of local vasodilatory substances directly affecting vasomotor tone or indirectly affecting blood flow via local peptinergic reflex areas (14, 31). This concept is certainly concordant with the studies and conclusion of Jacobson (33) and Augier (24) but in conflict with the conclusions of Tankel and Hollander (32) who noted secretion ceased when blood flow was interrupted but could find no correlation between blood flow and secretion following less drastic alteration in blood flow.

Conclusions

Using a double thermistor, tissue blood flow meter, the present experiments examined the relationship between pancreatic blood flow and pancreatic secretion stimulated or inhibited by secretin, PZ, and glucagon. The following conclusions were drawn from the results:

1) Under continuous stimulation of secretin, pancreatic blood flow showed a maximum increase of 27.5 percent about two minutes following the intravenous injection of 2 u/kg secretin and a maximum augmentation of 39.0 percent about two minutes following the injection of PZ. After 15−20 minutes, the pancreatic blood flow in both instances returned to control values. The increases and decreases of blood flow and the secretion showed sequential correlations.

2) Judging from the increment (or decrement) at 20 minutes after injection of the hormones,

the pancreatic blood flow and the secretion continued to demonstrate close relationship. This relationship could be stated mathematically by an equation which expressed the change in pancreatic blood flow as the sum of the percentage change in pancreatic secretory flow and the percentage change in pancreatic amylase output.

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Drug-Disease Interactions: A Review of the Literature

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Drug-drug interactions are well established. There have been many publications and computer programs to describe this effect. This manuscript deals with a related subject, that of drug-disease interactions. The majority of studies on medications have been undertaken in normal subjects or in those having an abnormality only in the target organ system. However, many patients have abnormalities of other organ systems which influence the efficacy, absorption, distribution and elimination of medication.

Several drug-disease interactions are well known—Propranolol and asthma, Gentamicin and renal insufficiency, and Digoxin and hypokalemia. In this paper, the common as well as the less common drug-disease interactions will be listed. If known, the nature and the degree of the interaction will be noted. We will review and discuss the most commonly used agents at The Mount Sinai Medical Center formulary.

Antibiotics

Aminoglycoside-antibiotics

Renal Disease: The aminoglycosides are not metabolized but are excreted by the kidney. The dosage should be adjusted with varying degrees of renal insufficiency (1).

Burns: The dose of tobramycin has to be changed for burns patients for the following reason: The glomerular filtration rate increases in patients with major burns. In one study (2), the glomerular filtration rate of burn patients was 172 ± 48 ml/min vs 125 ± 10 ml/min for control and correspondingly the half life of tobramycin decreased from 1.13 ± .14 to .85 ± .19 hr for burn patients. Nomograms have been developed for tobramycin use in burn patients (3).

Edema: In patients with demonstrable edema, the serum levels of the aminoglycosides may be lower than expected. As is the case with obesity, the lean body mass should be used to determine dosage (4, 5).

Hypoxia: There is some evidence of decreased clearance of amikacin in hypoxic children (6) and hypoxic rats (7).

Ampicillin

Absorption: The major portion of the penicillins are absorbed from the proximal portion of the small intestine although absorption may also occur more distally (8–10). The relative percentage absorption for ampicillin and phenoxymethyl penicillin (PCNV) are similiar (11). Some diseases of the small bowel influence ampicillin absorption, that is, increases in acute bacillary dysentery (12), but are uninfluenced by Celiac disease (13).

Renal Disease: The dose of ampicillin must be adjusted for renal insufficiency. The current recommendation is to increase the dosing interval from every 6 hours for creatinine clearance greater than 30 ml/min to every 12 hours for creatinine clearance below 15 ml/min (1). Urinary levels of ampicillin have been found adequate even in the presence of renal insufficiency (14).

Several workers have found circulating inhibitors of ampicillin albumin binding (15), a topic that will be further discussed in the section on oral anticoagulants. However, it is worth noting that since ampicillin is only 15%–20% protein bound, inhibitors of protein binding and hypoalbuminemia are not a major cause of abnormal ampicillin metabolism.

Cephalosporins

Absorption: The absorption of cephalexin is decreased by cystic fibrosis (18), achlorhydria (19),

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gastrectomy (19), celiac disease (by 20%–30%) (13) and in Crohn's disease (20%–30%) (21).

Renal Disease: The dosage of cephalothin should be modified for renal insufficiency. When the glomerular is 10-50 ml/min the dose should be 50% of the standard dose and when the filtration rate is less than 10 ml/min the dose should be 25% of standard (22–24).

Cephalosporin protein binding is reduced by 15% in patients with uremia (15) but this is of no clinical significance.

Liver Disease: The cephalosporins are metabolized by the liver. The biotransformation of the antibiotics, however, is unimpaired in patients with cirrhosis and chronic hepatitis (25). Biliary tract levels of cephalosporins are not higher than blood levels in patients with cystic duct obstruction (26).

Diabetes Mellitus: The cephalosporins may give a false positive reading for glucose on the Clinitest reagent.

Clindamycin

Renal Disease: There is no required change in dosage for renal dysfunction (1, 27).

Liver Disease: Hinthorn (28) gave 300 mg of clindamycin intravenously every 12 hours for two days to a group of patients with cirrhosis, acute viral hepatitis, and chronic hepatitis. There was no prolongation of the half-life in the group with active or chronic hepatitis when compared to controls. However, he did find a 39% prolongation of clindamycin half-life in patients with cirrhosis. Avant (29) found a 34% prolongation in the half-life of clindamycin in cirrhotics while Brandl (30) found a 100% increase. Williams (31) found that the SGOT increased during therapy with clindamycin though Hinthorn did not find this change. The current recommendations are not to alter the dose of clindamycin in liver disease though it should be kept in mind that the dosages given during the above studies were less than commonly employed.

Clindamycin is 90% protein bound but therapeutic efficacy or the occurence of adverse effects with decreased albumin has not been studied (32, 33).

Myasthenia Gravis: Clindamycin produces neuromuscular block. However, the drug interacts with the succinyl choline or curare block to only a limited extent hence its use in myasthenia is not a major problem (34).

Diarrhea: Tedesco (35) has reported the incidence of diarrhea to be as high as 10%–20% of patients and, in fact, the Physicians Desk Reference states that when diarrhea begins with the use of clindamycin the drug should be discontinued. Condon (36) treated patients with varying abnormalities with clindamycin. If the patients had diarrhea, the drug was discontinued. If required, the drug was restarted. The incidence of diarrhea in patients who had a history of clindaymcin-associated diarrhea was no higher than those who did not have this history. No patients in the study had pseudomembranous colitis. The presence of diarrhea, if proven not to be pseudomembranous colitis, is not a contraindication to the use of clindamycin.

There is no evidence that the use of clindamycin is associated with a higher incidence rate of adverse effects in patients with either regional ileitis or ulcerative colitis.

Erythromycin

Absorption: All erythromycin compounds are acid labile except for erythromycin estolate (37). A five fold increase in serum levels has also been shown for subjects with decreased acidity (38, 39). Decreased serum levels would be expected for patients with delayed gastric emptying or increased acidity.

There is no effect of Celiac disease on erythromycin absorption (13). Crohn's disease has been shown to decrease the serum levels and the 24-hour urinary excretion of erythromycin stearate by about 20% (21). Crohn's disease had no effect on the serum levels of erythromycin ethyl succinate (21).

Renal Disease: There is no change in dosage for renal disease (1).

Liver Disease: Erythromycin estolate use in patients with liver dysfunction is probably imprudent because of hepatotoxicity of the drug (40, 41).

Penicillin

Absorption: Patients with achlorhydria have been found to have decreased serum levels of penicillin (PCN) after oral doses (19). PCN V, though more stable than PCN G, is still metabolized in the stomach. The oral dose must be 3–5 times the intramuscular dose and this is only partially due to incomplete absorption (11). The relationship between blood levels can be expected with diseases which delay gastric emptying (43), while increased levels occur in states of diminished acidity, increased emptying time, gastrectomy or drainage procedure.

Patients with untreated celiac disease have serum levels of PCN which were less than 30%

that of controls (44) while patients with other forms of malabsorption have normal serum levels.

Lupinsky (19) determined the absorption of PCN indirectly (by measuring the amount of PCN excreted in the urine) and found that patients with acute and chronic disorders of the pancreas had reduced excretion. This reduction is not a result of abnormal micelle formation, as patients with obstructive jaundice have normal absorption of cephalexin, ampicillin and PCN (45).

Renal Disease: In end stage renal failure with creatinine clearance less than 15 ml/min, the PCN dosage interval should be increased to 6-12 hours (1) because of reduced excretion of the drug.

PCN binding to protein is decreased in azotemia (46–48). The degree of binding, however, is not correlated with the degree of azotemia. Craig (15) found a 30% reduction in PCN binding in uremia, a fact of little clinical significance.

Each million units of PCN contains 1.7 meg of potassium and this may cause elevation of serum potassium when high dose PCN is given to patients with end stage renal disease.

Liver Disease: PCN, being an acidic drug, is displaced from albumin sites by bilirubin. Bratlid (49) found that the binding to albumin was not affected to any significant degree by bilirubin levels up to 200 μmol/L.

PCN binding to albumin is variable, 20%–60% (24, 15) and is not significantly altered by hypoalbuminemia (17).

Antituberculous Agents

Isoniazid

Absorption: Hurwith (50) studied the effect of antacids on serum levels of isoniazid (INH). He found a decreased peak level and decreased levels at half, one, two and four hours after administration of oral INH with antacids. The lower levels were not due to an INH-Mg or Al interaction, but may have been secondary to delayed gastric emptying (43) though it is difficult to determine. In these studies, it has been found than once daily INH is more effective than a smaller dose given more often (51, 53). Maintenance of peak levels that are decreased by delayed gastric emptying is apparently the important factor in effective use of the drug.

Renal Disease: Renal insufficiency prolongs the half-life of INH in slow acetylators (54, 55). There is no data to indicate that the prolongation is of any clinical significance or that dosage should be altered (1).

Liver Disease: INH has been shown to alter liver function tests and in some cases to produce hepatic failure (56). Whether hepatic failure occurs more often in patients who have hepatic disease prior to therapy is still unanswered. In 68 patients with chronic liver disease given INH, Levi (57) found increased liver toxicity.

The current recommendation is to consider the presence of abnormal liver function test a relative contraindication to INH use. A major problem appears to be lack of knowledge as to whether the abnormal tests are spurious, secondary to INH when it occurs in a patient older than 40 years, four to eight weeks after initiation of treatment, or lasts for greater than four weeks.

Acetylator Status: Recent studies have not shown change in hepatotoxicity when INH is rapidly acetylated (58).

Cardiovascular Agents

Alpha Methyldopa

Liver Disease: As was the case with isoniazid, alpha methyldopa can cause abnormal liver function tests and in certain cases cause hepatic failure. Though the actual incidence of hepatic failure following use of the drug in patients with preexisting liver disease is not known, it is probably prudent to withhold it in such patients (59).

Hematologic Disorders: In one study (50), alpha methyldopa was the most frequent cause of acquired hemolytic anemia as well as the most frequent cause of death among patients with hemolytic anemia. It is therefore prudent to withhold the drug from patients with a history of autoimmune hemolytic anemia.

Renal Disease: The dosing interval should be increased in patients with renal insufficiency. If the glomerular filtration rate is between 10 and 50 ml/min the dosing interval should be 9–18 hours and for less than 10 ml/min the interval should be increased to 12–24 hours.

Digitalis

Absorption: Heiser (61) showed that serum levels of digoxin measured 12 hours after dosing were 33% that of controls in patients with a variety of malabsorption syndromes including small bowel resection, laxative abuse, celiac disease and neoplasm. Pancreatic insufficiency was not associated with a decreased serum level of digoxin. Hall (62), in his study of malabsorption syndromes found only a slight increase in fecal excretion of 3H-Digoxin vs. controls. Serum levels were only different at 90 and 120 minutes after dosing and similar at other times. Absorption was not impaired by congestive heart failure in at least one study (63), or by gastrectomy (64) or jejunoileal bypass (65).

Renal Disease: The dosage of digoxin may have to be altered for renal insufficiency (1). The dose should be reduced to 25%–75% of the standard dose for glomerular filtration rate less than 50 ml/min and 10%–25% of standard dose for glomerular filtration rate less than 10 ml/min. Obtaining serum level of digoxin 12 hours after the last dose is helpful.

Serum levels of digoxin are decreased in hyperthyroidism and increased in hypothyroidism due to the effects of thyroid hormone on glomerular filtration rate (66, 67). This may in part explain the clinically observed need in hyperthyroid patients for large doses of digoxin to control their arrhythmias (68).

Liver Disease: Zilly (69) did not find any difference in digoxin pharmacokinetics in patients with viral hepatitis vs. controls.

Cardiac Disease: Congestive heart failure with edema may dilute the serum levels of digoxin and the levels may increase when the congestive heart failure subsides (70, 71).

Pulmonary Disease: The use of digoxin in corpulmonale has been reviewed by Doherty (72), and its indications will not be reviewed here. Kirby (73) and Goldberg (74) have shown that hypoxemic patients on digoxin have an increased frequency of arrhythmias over those not on the drug.

Fluid or Electrolyte Disorders: The incidence of arrhythmias increases above controls when digoxin is used in patients with hypokalemia, hypomagnesemia or hypercalcemia. There is no effect of diabetes insipitus on digoxin pharmacokinetics (75).

Propranolol

Absorption: Propranolol levels are increased in patients with active celiac disease (24), or in those patients who have been under treatment for less than one year. Patients in remission have the expected serum levels (76). In patients with regional ileitis the serum levels of propranolol are three times that of control.

Renal Disease: Lowenthal (77) initially found 2–3 fold higher levels of propranolol in patients with end stage renal disease who were given single doses of the drug. However, when multiple doses were given, the serum levels fell to normal. Lowenthal attributed these changes to enzyme induction. The current recommendations do not require adjustment of propranolol dose, except when the glomerular filtration rate falls below 10 ml/min (1).

Liver Disease: Branch (78) found that the clearance of propranolol was decreased by 52% in cirrhosis and 40% in chronic active hepatitis. In each case, the volume of distribution was increased by about 100%, thus the therapuetic effect was unchanged. Wood (79) found that the unbound concentration of propranolol in steady state therapy in patients with cirrhosis was higher than controls.

Cardiovascular: The following are considered to be relative contraindications to the use of adrenergic blocking agents beta blockers: Raynaud's phenomenon, Buerger's disease and mild congestive heart failure. More severe contraindications include severe congestive heart failure, not secondary to an arrhythmia, cardiogenic shock, heart block greater than first degree and slow bradycardia (80).

Respiratory: Relative contraindications to beta adrenergic blocking agents are a history of chronic obstructive pulmonary disease and a more severe contraindication is an episode of acute asthma (80).

Endocrine: A relative contraindication is diabetes mellitus without a history of hypoglycemia while a severe contraindication is unstable diabetes with a history of hypoglycemia since signs and symptoms of hypoglycemia are masked by beta adrenergic blockage (80).

The findings in patients with hyperthyroidism are conflicting. One author (81) has found an increase in the clearance of propranolol after oral dosage while others have found no difference (82, 83).

Diuretics

Furosemide

Absorption: Absorption of furosemide is proportional to the clearance of the drug, which is proportional to the (85) glomerular filtration rate. The effects of furosemide are reduced by left sided congestive heart failure (86), anuric renal failure (87) and the hepatorenal syndrome (88).

Thiazide Diuretics

Absorption: The absorption of thiazide diuretics is reduced by 50% in patients who have undergone jeuno-ileal bypasses (89).

Congestive heart failure: The naturetic effect of thiazide diuretics correlates with their urinary excretion. In congestive heart failure, the half-life is prolonged and hence higher doses are required for a therapeutic response (90).

Other: The thiazides alter the glucose tolerance test. They are considered contraindicated in patients with hypercalcemia since they have a parathyroid-like effect on the distal tubule and cause reabsorption of calcium, thereby aggravating hypercalcemia.

Oral Anticoagulants

Coumarins

Renal Disease: Coumarin oral anticoagulants have been found to bind to albumin less extensively in uremic patients (91, 92), and the decreased binding increases the free fraction by about 30% (91). However, Bachman also noted that the half-life of the oral anticoagulants was decreased. Bachmann (92) and Sachs (93) have shown that in uremia the usual dose of oral anticoagulants should be the same as controls. This problem has been reviewed (94).

Liver Disease: Viral hepatitis has been found to increase the sensitivity of some but not other patients to oral anticoagulants (95).

At serum warfarin concentrations of 1 μg/ml, the range of bound warfarin is estimated to be 98.11%–99.45% (96). This apparently small difference actually represents a four fold range in the unbound serum levels of warfarin. The extent of binding is constant at therapeutic levels for the same individual (97). Kawai (98) has found that increasing the serum albumin levels does not affect warfarin sensitivity. Before the steady state is reached, the presence of hypoalbuminemia causes a greater peak effect and decreases the half-life (99). Hypoalbuminemia does not imply an increased sensitivity but a changing albumin concentration (1 gram/dl) may affect the prothrombin time adversely.

The presence of malabsorption with decreased Vitamin K levels may increase patient sensitivity to oral anticoagulants.

It is well known that sulfonamides can displace bilirubin from binding sites in children and produce kernicterus. Wingard (100) demonstrated that the free fraction of dicoumarol could be increased by 34% and 81% when bilirubin was added to serum in concentrations of 5 and 11 mg%.

Diabetes Mellitus: The oral anticoagulants, being acidic drugs, are displaced from binding sites on albumin by other acidic drugs. The presence of acidemia during diabetic ketoacidosis can also be expected to displace the oral anticoagulants from their binding sites.

Thyroid Disease: Solomon and Schrogie (101) have shown that increased serum di-thyroxine levels can potentiate the anticoagulant response to dicoumarol. This in vitro study has been substantiated by a case report (102). The effect is believed to be due to the thyroid enhanced degradation of Factor II rather than a direct effect on drug half-life.

Congestive Heart Failure: Congestive heart failure has been reported to be accompanied by an increased effect of dicoumarol (103). This effect is not caused by a change in the half-life (104), but by a redistribution of body water (94).

Other: Oral anticoagulants should be considered relatively contraindicated in patients with a history of bleeding ulcer disease, abnormal platelets or bleeding disorder. They are strongly contraindicated in patients with active ulcer disease or history of life threatening hemorrhage.

Xanthines

Theophylline

Liver Disease: Since theophylline is mainly metabolized by the liver, it is worth briefly reviewing the various classifications of liver metabolism (105). Hepatic metabolism may be either: A-microsomal or B-nonmicrosomal. Within each group, the rate of metabolism is dependent upon A-flow or B-capacity. In flow limited drugs (A), the rate of metabolism is limited by the amount of drug presented to the liver. Hence, the metabolism varies with the hepatic blood flow. In the capacity limited drugs (B), the rate of metabolism is limited by the ability of the liver to metabolize the drug and not limited by the blood flow. Within the capacity limited group, there are drugs in which the rate of metabolism is dependent upon albumin binding and others in which rate is independent of albumin binding. In hepatic dysfunction, the drug disposition rate can not be predicted accurately just from the characteristics of its liver metabolism. Vesell (106) found that there was no correlation in the rate of metabolism of three drugs which all used the microsomal system and had low extraction ratios (were capacity limited). Hence, there will be no attempt to generalize from drug models to theophylline or other specific drugs in this paper.

Piafsky (107) administered single intravenous doses of theophylline to nine patients with alcoholic cirrhosis and nineteen controls. They found prolongation of half-life in the cirrhotics (25.6 hrs vs. 6.7 hrs) and lower binding to albumin (36.8% vs. 52.6%). Changes in the liver blood flow appear to have little effect on the clearance of theophylline which is a drug with a low extraction ratio (108, 109). In a study of 43 older, acutely ill hospitalized patients with chronic obstructive pulmonary disease, treated with intravenous aminophylline, the clinical diagnosis of liver disease was associated with a higher rate of adverse effects (110). Thus, the current recommendation for a single loading dose of aminophylline for patients with hepatic dysfunction is 6 mg/kg IV over twenty minutes. A nomogram has been published by Jusko (111).

Absorption: The theophylline preparations are well absorbed and there are no reports of any disease state causing drug malabsorption. They should probably be given with antacids in the case of active ulcer disease or active gastritis.

Renal Dysfunction: No change in dosage is necessary for renal insufficiency.

Cardiac Disease: In several studies (112, 115), the presence of cardiogenic pulmonary edema prolonged the half-life of theophylline by about 40%.

Pulmonary Disease: Powell (113) determined theophylline clearance in patients with pneumonia and found it decreased by about 40% below the normal of 9 mg/kg/hr. Chronic obstructive pulmonary disease has also been found to decrease the clearance of theophylline for other reasons perhaps due to a depressant effect on the liver of hypoxemia (110).

Anticholinergics

Propantheline

The use of anticholinergic agents is relatively contraindicated in the presence of narrow-angle glaucoma, atrial flutter, paroxysmal atrial tachycardia with block and obstruction of the gastrointestinal tract (gastric outlet obstruction, colon cancer, diverticular disease) and urinary tract (benign prostatic hypertrophy) (116).

Locally Acting Gastrointestinal Agents

Antacids

Renal Disease: The magnesium containing antacids are considered strongly contraindicated in patients with end stage renal disease.

Liver Disease: The antacids containing a large amount of sodium are considered relatively contraindicated in patients with cirrhosis or congestive heart failure.

Gastrointestinal Disease: The aluminum containing antacids are considered relatively contraindicated in patients with anal fissures or hemorrhoids as their tendency to cause constipation may aggravate these. In patients with a history of prolonged constipation, aluminum containing antacids may cause impaction.

Bulk Formers or Stool Softeners

Gastrointestinal Disease: The bulk forming laxatives, Bran, Methylcellulose and psyllium preparations are generally devoid of systemic effects. Patients who have difficulty swallowing should be warned not to take these preparations dry, and generous amounts of water should be prescribed. Occasional cases of esophageal obstruction have been reported in patients with dysphagia (116). Both groups should be considered contraindicated in patients with acute abdominal pain until diagnosis has been determined (117).

Cimetidine

Renal Disease: The dose of cimetidine should be altered to 300 mg every 12 hrs in patients with glomerular filtration rates less than 30 ml/min (1).

Hormones and Hormonal Agonists

Glucocorticoids

Absorption: Oral prednisone has been shown to be completely absorbed in patients with chronic liver disease and in controls (194).

Renal Disease: There is no change in dosage with end stage renal disease (1).

Liver Disease: Powel and Axelson (118) have shown that the 11-keto reduction of prednisone to the active agent prednisilone is impaired in patients with active liver disease. Davis (119) has shown that the clearance of prednisilone is decreased in patients with active liver disease though bioavailability is the same.

Major side effects of glucocorticoids are more prevalent in patients with liver disease and hypoalbuminemia, who are treated with steroids (120, 121, 71). Any disease that lowers albumin levels can be expected to increase the incidence of glucocorticoid side effects (99, 122).

Endocrine Disorders: The anti-insulin properties (123) of steroids should be kept in mind when therapy is being initiated with steroids or in a patient who is well controlled on an anticoagulatory regimen and treatment with steroids is being initiated.

The clearance of cortisol is affected by thyroid hormone. In response, the secretion of cortisol is increased in hyperthyroidism and decreased in hypothyrodism (124, 125). The effect of thyroid hormone on the metabolism of synthetic glucocorticoids has not been well studied, but is probably similar to that of hydrocortisone (125).

Cardiovascular: The mineralocorticoid effects of the steroids can aggravate hypotension and antagonize the effects of antihypertensives, especially diuretics.

Respiratory Disease: Isoniazid prophylaxis should be initiated in patients being given steroids who have a history of a positive PPD. There have been no randomized trials of this and the need for prophylaxis has been questioned (126).

Gastrointestinal Disease: In patients with active gastritis or peptic ulcer disease, steroids are best used with an antacid.

Oral Contraceptives

Liver Disease: Those women who develop jaundice during pregnancy or following oral contraceptive use are all believed to have had decreased bilirubin excretion prior to the onset of hypoalbuminemia. The major dilemma in giving these patients oral contraceptives is not the increase in bilirubin but the belief that a more severe hepatic derangement is present (127). Patients with Dubin-Johnson syndrome are also at risk for developing increased levels of bilirubin (127).

Increased levels of bilirubin following oral contraceptives use have also been reported in patients with cirrhosis (126).

Oral contraceptives should be avoided during the acute stages of viral hepatitis as they may prolong the period of cholestasis (128).

Hepatic cell adenomas have been reported to regress with the discontinuation of the oral contraceptives and to grow when the drug is continued (127).

Cardiovascular Disease: The presence of hypertension increased the incidence of thromboembolism and hemorrhagic strokes. The use of oral contraceptives in patients with hypertension further increases the incidence of strokes (129). Oral contraceptives have also been found to increase the cardiac output and stroke volume and can cause fluid retention. Their use in patients with borderline compensated congestive heart failure secondary to congenital and rheumatic heart disease should be restricted (130).

Migraine Headaches: Reports have shown that the presence of migraine headaches increases the incidence of strokes in women who suffer from them (129, 131, 132); the use of oral contraceptives further increases this incidence. Ryan (133) has found an exacerbation of migraine symptoms in patients with migraines who were treated with oral contraceptives.

Carbohydrate and Lipid Metabolism: Studies by Stiendel (134) and Menear (135) demonstrate no significant change in the daily insulin requirement of women who used oral contraceptives containing either nortestosterone or 17 alpha acetoprogesterone. The effects of the agents on plasma glucose are small (136, 135) and completely reversable on their discontinuation (136). The effects of the agents on triglyceride and cholesterol metabolism have been extensively reviewed by Beck (137). The effect on triglycerides and cholesterol are variable (137) and long-term effects in patients with elevated triglycerides, cholesterol, blood pressure or serum glucose are uncertain.

Estrogen Dependent Cancer: Oral contraceptives are relatively contraindicated in patients with endometrial and breast cancer.

Patients having fibrocystic disease of the breast who take oral contraceptives have been found to have an increase in the rate of breast cancer (138) but this has not been confirmed (139).

Oral Hypoglycemics

Renal Disease: Chlorpropamide is contraindicated in patients with glomerular filtration rates less than 50 ml/min while tolbutamide's dosage is unchanged in renal disease (1).

Liver Disease: Tolbutamide clearance was found to be increased by 275% in one study of patients with acute viral hepatitis (138) but another study (141) found no difference in tolbutamide clearance with this disease.

There is no effect on tolbutamide's half-life in cirrhosis (142). A larger free fraction of tolbutamide can be measured in hypoalbuminemic states but the higher rate of elimination compensates for this.

Cardiac Disease: Oral hypoglycemics have been found to increase mortality from atherosclerotic heart disease (144).

Thyroid Disease: Hypothyroidism decreases the half-life of tolbutamide and the half-life returns to normal when the disease is controlled by propylthiouracil (145).

Pulmonary Disease: Sotaniemi (146, 147) has shown a 33% decrease in the tolbutamide half-life for patients with chronic hypercarbia and hypoxemia, and hospitalized asthmatics. However, in both studies, the control group was not taking the same other medications as the index patients.

The decrease in the tolbutamide half-life may be secondary to hypoxia, hypercarbia or the medication inducing the microsomal system of the liver.

Thyroid Hormone Replacement

Addison's Disease: The use of thyroid hormone replacement is strongly contraindicated in the presence of untreated Addison's Disease.

Other: Insufficient doses of thyroid hormone replacement produce myxedema and toxic doses produce thyrotoxicosis. The effect of these disease states is listed under each individual drug (digoxin, propranolol, oral anticoagulants, oral hypoglycemics, corticosteroids and barbituates).

Antiinflammatory Agents

Nonsteroidal Antiinflammatory Agents

Gastrointestinal Disease: The erosive effects of the nonsteroidal antiinflammatory dosage except for aspirin, occur whether the drugs are given orally or subcutaneously (148). In patients with active ulcer disease or gastritis, these dosages should be given with antacids, even if they are administered rectally.

Renal Disease: No alteration of the dosing regimen of indomethacin is required for renal failure. The ibuprofen dosing interval should be increased to every eight hours for glomerular filtration rates of 10–50 mg/min and to every 12 hours for glomerular filtration rates less than 10 ml/min (1).

Respiratory Disease: Naprosen and its cogeners have been found to induce acute attacks in asthmatics sensitive to aspirin (149).

Hematologic Disease: Bleeding times of patients given 3.6 grams of aspirin and 500 mg of naprosen were compared. The two groups were similar and abnormal two hours after treatment. The nonsteroidal antiinflammatory agents should be used cautiously in patients with platelet disorders or bleeding diathesis (150).

Anticonvulsants

Barbiturates

Renal Disease: The protein binding of phenytoin is decreased in uremia. This is partially besame, but the dosing interval of phenobarbital should increase from every eight hours to every 8–16 hours for glomerular filtration rates less than 10 ml/min (1).

Liver Disease: The half-life of phenobarbital increases from 86 hours to 130 in patients with cirrhosis (149). However, patients with acute viral hepatitis had normal half-lives.

The metabolism of amobarbital (152) and hexabarbital (153) is also impaired by liver disease.

Sessions (154) did not find an increase in the sensitivity of patients with cirrhosis to pentobarbital despite the prolonged half-life and the clinical belief that cirrhotics have an increased sensitivity to the central nervous system depressant effects.

Respiratory Disease: Barbiturates are relatively contraindicated in chronic obstructive pulmonary disease because the agents are respiratory depressants.

Depression: The barbiturates are a common means of suicide in depressed patients (155). Safer agents should be used when necessary on such patients.

Phenytoin

Renal Disease: The protein binding of phenytoin is decreased in uremia. This is partially because of lower serum albumin levels in patients with renal disease and partially because of an irreversible binding inhibitor (9, 11). Though the free fraction is increased, the dosage need not be altered since reports have shown that both drug metabolism and the volume of distribution are increased (156, 157).

Liver Disease: The complete pattern of interaction between phenytoin and liver diseases has not been fully elucidated. The current recommendation is to monitor serum levels when liver disease is present. Kutt (158) has shown an accumulation of unmetabolized drug in patients with liver disease. Blaschke (150) showed an increase of 20%–40% in the phenytoin clearance in patients recovering from acute viral hepatitis. The same study showed a decreased clearance in patients who had not yet recovered. Hooper (160) found plasma protein binding of phenytoin to be decreased in patients with cholestasis and the degree of binding was inversely correlated with the serum bilirubin.

Affrim (161) has found that binding in patients with alcoholic liver disease is normal, where as others have found it to be decreased (160, 162). Mild degrees of hypoalbuminemia may double the free concentration of phenytoin (163).

Orthopedic Diseases: Phenytoin predisposes to metabolic bone diseases. It is currently believed that this effect is caused by decreased vitamin D levels which in turn is caused by an increase in hepatic microsomal metabolism of vitamin D to all other metabolites but 25-OH Calciferol (164). Hence, use of the drug in patients with rickets, osteomalasia and malabsorption syndromes should be supplemented with oral vitamin D.

Hematologic Disorders: Phenytoin decreases folate levels though the effects of folate supplementation have varied. Some anemic patients have had exacerbations of convulsive disorders while others have improved, when treated with supplemental folate (165, 164).

Psychotropics

Benzodiazepams

The pharmacokinetics of the benzodiazepams are complex. The drugs as well as some of the metabolites are active, and are excreted at different rates. The subject has been reviewed by Hoyumpa (167).

Absorption: In chronic alcoholic cirrhotics the absorption of diazepam is decreased by 44% (168).

Renal Disease: Protein binding of diazepam is decreased from 98% (169) to 92% in uremics. The clinical importance of this is not clear and Bennett (1) has not recommended a change in dosage for end stage renal disease.

Liver Disease: Andreasen (170) and Klotz (171) found an increase in the serum half-life of diazepam in patients with acute viral hepatitis, chronic hepatitis and cirrhosis. Roberts also found this to be true in patients given chlodiazepoxide (172). The impairment of diazepam elimination is reversable in patients with viral hepatitis. Half-life of the drug returns to normal but slower than in the bilirubin and SGOT (171). In patients with cirrhosis and a history of hepatic encephalopathy, Murry-Lyon (173) found an increased sensitivity to diazepam. A higher rate of adverse effects of the benzodiazepam occurs in patients with decreased albumin levels. The number of patients with liver and renal disease in both groups was the same (174).

Phenothiazines

Renal Disease: No change in dosage of these agents is necessary for end stage renal disease (1).

Liver Disease: A phenothiazide was administered to patients with compensated cirrhosis and matched controls (175). No significant difference was found in plasma levels and there were only minimal differences in the elimination rate. Cirrhotics demonstrate increased sensitivity to the phenothiazines which is believed to be due to altered neurologic responsiveness.

Respiratory Disease: The phenothiazines have marked sedative properties and hence should be used cautiously in patients with chronic obstructive pulmonary disease.

Cardiovascular: Because of their anticholinergic effect, phenothazides should be used carefully in patients with atrial flutter and paroxymal atrial tachycardia with blocks. The drugs have been reported to cause marked hypotension in patients with pheochromocytomas (117).

The phenothiazines may cause cerebrovascular accidents in patients with marked cerebrovascular disease secondary to their hypotensive effects and various adverse cardiovascular effects in patients with heart disease.

Tricyclic antidepressants

Cardiovascular: The cardiovascular side effects and interactions of tricyclic antidepressants are secondary to anticholinergic effects (previously mentioned) and to direct effects on the heart and conduction system.

In one study of patients with acute cardiac disease (175), there was an increased incidence of sudden death in those who were treated with antidepressants. The Boston Collaborate Drug Surveillance Program did not find an increase rate of cardiotoxic events in patients treated with the tricyclic antidepressants (177). Schrieber (178) and Goldberg (179) have treated patients with these agents who had ventricular premature complexes, atrial premature complexes, atrial filrillation, left bundle branch block, sinus tachycardia and acute myocardial infarction without complications.

Neurologic Disorders: The tricyclic antidepressants have been reported to lower the seizure threshold in patients with a history of a convulsive disorder (117).

Psychologic Disorder: The tricyclics have been reported to convert the depressant phase of manic-depressant illness to the manic phase (117).

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Theodor Billroth

The Life of a Surgeon in the Spirit of Music

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Beginnings

Theodor Billroth ranks among the most prominent figures in the history of medicine and science of the nineteenth century. He acquired worldwide fame as the founder of modern abdominal surgery, as a brilliant medical educator, and as the author of numerous works, including the first textbook of surgical pathology. In his day, he was widely esteemed for his musical abilities, both as a performer and a critic. The annals of intellectual history cite him as a close friend of Johannes Brahms and as the author of a book about musicality in man.

Billroth's musical roots reach back into his ancestry. His paternal grandfather, Johann Christian Billroth, a successful lawyer and for a quarter of a century the mayor of Greifswald, a small university town in northern Germany, regularly united the city's leading musical personalities at his house. His maternal grandmother, Dorothea Willich, who took great interest in the boy's musical education, had been a celebrated soprano at the Berlin National Opera, where she had participated in the premier performance of Beethoven's Fidelio. Music had likewise played a dominant role in the life of Billroth's father, Karl Theodor, a Lutheran minister, who died in 1834 at the early age of 34. Later, Billroth summarized his artistic background in a letter to Hanslick, "Thus I am a child of music and the theater" (1).

Billroth's musical heritage, however, extended beyond the realm of his family and the trends of his day. Keenly aware of the role of tradition in art, which he compared in importance to heredity in nature, Billroth was a product of the musical tradition of northern and central Germany. In that region, unlike in Austria with its aristocratic maecenas, the interest in music and the material support for musical activities came from prominent citizens, like Billroth's grandfather. Music was not merely a pastime, enjoyed by the leisurely classes, but an integral part of community life. This tradition was reinforced by the great concern for music within the Lutheran church. Billroth repeatedly emphasized that Protestant church music had exerted a decisive influence on him. With social conditions so favorable to music, it is not surprising that northern and central Germany during the 17th and 18th century produced such great composers as Schein, Scheidt, Schuetz, Buxtehude, Pachelbel, Telemann and, above all, Johann Sebastian Bach and Handel. In addition, lesser masters—Matheson, Keiser, Hasse, Graun, Scheidemann, Reinken, and Stamitz—contributed to a flourishing musical life, of which Billroth was a product and whose tradition he recalled throughout his life.

Christian Albert Theodor Billroth, the eldest of five sons, was born on April 26, 1829 on the Baltic Island of Ruegen. After his father's death, the family, largely dependent on support from relatives, settled at Greifswald.

Music flourished in Billroth's childhood environment. The entire family and numerous friends participated in performances of chamber music, oratorios and operas. Thus, Billroth's musical talent, which expressed itself at an early age, by no means isolated him from his surroundings or prevented a healthy interaction with his peers. The spirit of music united family and friends, adults and children alike.

By his late teens, Billroth had achieved a re-

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markable mastery at the piano. He had demonstrated an unusual vocal talent in numerous amateur performances of operas and oratorios, and he had composed a number of songs for various occasions. Additionally, he had acquired an extensive knowledge of musical literature, an arduous task demanding long and patient hours of thorough perusal of musical scores without the benefit of a radio or phonograph.

As an elementary and high school student, the boy performed below average. Particularly weak in mathematics and foreign languages, he needed a private tutor to meet the requirements of public school. Next to music, only history and literature aroused his interest. Upon graduation from high school, he summarized his plans for the future in a customary open letter to the faculty. He described himself as a below average student who had been constantly distracted from his work by his musical activities. In the same letter, he emphasized his early inclination toward the art of drawing and his deep interest in Homer's Odyssey (2).

With his extraordinary musical talent, reinforced by a thorough knowledge of music theory and history, it would seem only natural that the 19-year-old high school graduate, when selecting a university curriculum, opted for music. However, several family members, including his mother and his Uncle Seifert, a professor of pharmacology, and Wilhelm Baum, a surgeon and family friend, influenced the boy toward a medical career. As a result, Billroth informed his teachers of his intention to enter medical school at the University of Greifswald (3).

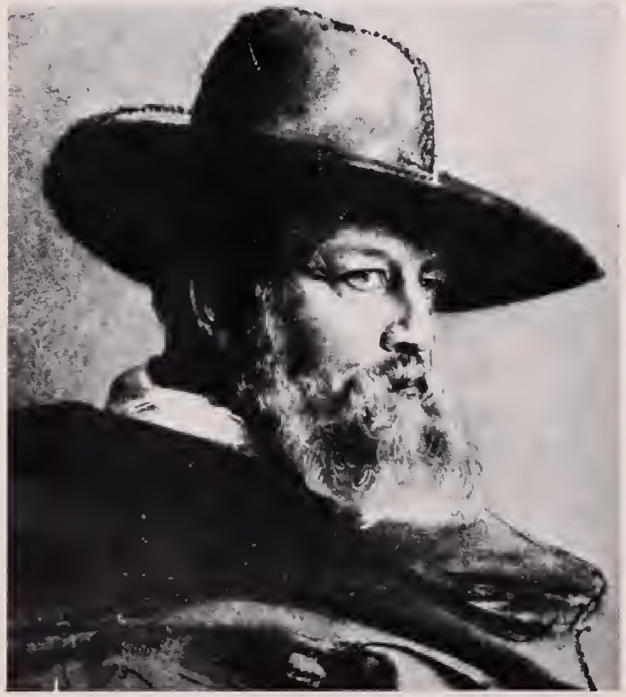

FIG. 1. Theodor Billroth in a portrait by Lenbach, the renowned 19th century portraitist.

How little this decision initially corresponded to an intellectual and emotional reality became apparent during the first semester. Billroth showed a total lack of concern for his studies and occupied himself entirely with music and social activities. After that initial period, however, he underwent a remarkable evolution and developed, in the course of only a decade, from a noncommitted student with a shallow interest in medicine to one of his generation's greatest medical scholars, practitioners, and educators.

Although the circumstances that catalyzed this unusual development are not completely known, a number of formative experiences can nevertheless be singled out. It is likely that, following the departure from his childhood sphere of family and friends, the young Billroth developed, and acquired a sense of independence which substantially solidified his attitude toward his future and toward medicine. His transfer, after one semester, from the provincial university at Greifswald to Goettingen, one of the great European centers of learning and liberal thought, was undoubtedly a formative experience.

Prior to Billroth's arrival, Goettingen had been a nucleus of social ferment and upheaval for several decades. In 1833, several professors, who almost instantly became known as the Goettingen Seven, had been summarily expelled from the university as a result of their protest against the arbitrary suspension of a liberal constitution by Ernst August, King of Hanover. Among the seven were some of the most brilliant minds of the day, such as Jakob and Wilhelm Grimm. Later Billroth wrote to Brahms, "When I was a student at Goettingen, from 1849 to 1850, the episode of the seven professors was still very much alive at the university" (4).

Billroth's gradually emerging emotional and intellectual bonds to medicine were reinforced by Baum, the surgeon and family friend. A gifted educator, Baum showed great concern for his students in professional as well as personal matters (5). His competence as a teacher and his congenial personality seem to have made a lasting impression on young Billroth, who referred to him as the founder of his scientific career (6). A letter written 21 years later from a resort in the Alps bears eloquent witness to Billroth's feelings of gratitude.

> "My dearly beloved teacher and friend,
>
> I have waited until the beginning of my vacation here in the mountains before answering your letter of May 15th.

> Many thanks for the excellent photograph of you. I look at it with sincere gratitude for all the beautiful and good things I owe you. You were indeed the first to place the spark of enthusiasm into my still waivering soul and vacillating personality. . . . I also saw, by your example, that it was possible to integrate art and science and that, in fact, a knowledge in the arts could serve to intensify the teaching of science" (7).

This last remark reflects Billroth's lifelong credo that art and science are rooted in the same soil, and emphasizes Baum's role in reinforcing that notion.

As a medical student, Billroth became earnestly involved in physiologic research under the guidance of Rudolf Wagner, the well known physiologist, whose impact on his career he described as "extraordinary" in the above letter to Baum. Together with his friend Georg Meissner (1829–1905), who later succeeded Wagner at Goettingen, and who is remembered today for his description of the tactile sense receptors (Meissner's corpuscles) and the innervation of the intestine (Meissner's plexus), Billroth occupied himself with the physiology of the nervous system of the electric ray. The two showed such proficiency at Wagner's laboratory that their teacher invited them, in the autumn of 1850, to accompany him on a scientific journey to Triest. At Triest, they met the eminent physiologist Johannes Mueller. In Vienna, Billroth first became acquainted with the university to whose fame he later so greatly contributed.

The transfer to the University of Goettingen and a concomitant emancipation from his family; the confrontation with critical social and political issues at Goettingen; the encouragement by Baum; the challenge of research at the laboratory of Wagner during his medical studies: all those factors seem to have been important in the decision to pursue his medical studies. However, the most essential reason for his commitment to medicine may very well have grown out of a critical evaluation of his musical talent. There is little doubt about Billroth's genuine musical gifts, as revealed in his work as a composer, instrumentalist and critic. His commitment to music, both intellectually and emotionally, during his teenage period is unquestionable. But upon leaving the realm of his youthful endeavors, he very likely engaged in a more detached evaluation of his talents. The result may have been an honest admission to himself that he lacked musical genius. Throughout his life Billroth retained a significant silence, at least so far as his published statements indicate, about his change from music to medicine. As a tacit admission of his musical shortcomings, he later destroyed all his compositions, which he described as awful stuff that stank dreadfully as it burned (8). Only a few humorous occasion pieces remained that were, in his words, the childish weaknesses of a dilettante composer (9). Yet the touch of frivolity in that statement does not conceal the fact that Billroth was particularly sensitive and perhaps even bitter in applying the word dilettant to himself. In a letter to Brahms about value systems in music, he distinguished between the genuine mind of a true artist and the vicarious approach of a dilettant like himself. He further restricted his own ability of musical understanding by quoting Schumann's famous statement that only a genius can fully comprehend the work of a genius (10). Thus, it may well be one of the great ironies in the history of medicine, albeit not open to verification, that Billroth's leading achievements as a surgeon, scientist and educator were the result of a resignation on the highest level, concluded by an unusually creative mind at a moment of critical confrontation with his own limitations. Lest such a view appear excessively speculative or pessimistic, one may recall Billroth's own statement about the positive value of resignation. "Resignation, unfortunately, constitutes an essential part in the harmonious perfection of human activities, unbearable, but unavoidable" (11).

Despite intensive studies and time consuming research, Billroth immersed himself deeply into the musical life of Goettingen. Together with Meissner, who appeared to attract him as much for his love of music as for his interest in science, he frequented concerts and operas. He participated in numerous student gatherings as a pianist or vocalist, and he composed festive songs for some of those events. With a befriended singer, Billroth rehearsed the title role of the oratorio Paulus by Mendelssohn, who, throughout his life, remained one of his favorite composers. When the famous soprano Jenny Lind quite unexpectedly accepted an invitation by the student body, Billroth was chosen to accompany her recital on the piano. He related that event in an effusive 5000-word letter to his mother. Though written with unreflected spontaneity, the letter foreshadows his analytical faculties and his talent of precise verbal communication that later earned him the reputation of a highly discerning music critic whose caustic pen (an epithet of Eduard Hanslick's) aroused general attention (12).

Billroth's musical interest at that time centered around Bach, Mozart, Beethoven and Mendelssohn. Schumann, whose works he later greatly admired, was almost unknown in northern Germany, nor had the young Brahms emerged on the musical scene.

Professional Groundwork

In autumn 1850 Billroth moved from Goettingen to Berlin, a cultural and political center and a major focal point of medical science in Europe. He received his medical degree from the University of Berlin in 1852. After a period of traveling that led him to Vienna and Paris, he returned to Berlin with the intention of settling there as a general practitioner. After two months, he abandoned that career without success. He accidentally met an almost forgotten friend from his hometown, who informed him of a vacancy as an assistant to Bernhard Langenbeck, one of the eminent surgeons of the time. Billroth applied and was accepted.

Langenbeck seems to have recognized the young man's potential immediately. Within a short time, Billroth had gained his confidence and trust to such an extent that, during Langenbeck's absence, the major responsibilities in clinic and classroom were relegated to him.

In addition to his duties in surgery, in pre- and postoperative patient care, and in teaching, Billroth dedicated considerable time to laboratory research. The publication of some two dozen scientific papers and a book about pathologic histology (13) constitutes impressive evidence of his accomplishments in research and writing during his Berlin years. Besides surgery, Billroth showed great interest in ophthalmology. He regularly attended lectures and clinical demonstrations by the famous ophthalmologist Albrecht von Graefe. Impressed by Billroth's talent, von Graefe gave him the opportunity of independent clinical work in ophthalmology. Later, in recommending Billroth for the chair of surgery at Zurich, von Graefe noted the young man's foresight, extraordinary competence and dynamic personality. He emphasized his teaching ability and his unusual adeptness at communicating with students (14).

After only three years with Langenbeck, Billroth, at the age of 27, advanced to the position of associate professor of surgery. Bernhard Langenbeck, with his extraordinary intellect, undoubtedly constituted a major influence on Billroth's lifelong undiminished dedication to surgery. Billroth repeatedly expressed his gratitude and his admiration for his great teacher. Langenbeck, in turn, paid his former assistant a major tribute when, in 1882, he proposed Billroth as the only candidate to succeed him. The Medical Faculty accepted his proposal unanimously and without discussion. Langenbeck remarked in a letter to Billroth, "This, to my knowledge, has never before happened at the Medical Faculty in Berlin. It should be a source of joy to you because you owe this unanimity in no way to my influence, which I never possessed in the Faculty, but exclusively to your prominence in the world of science" (15).

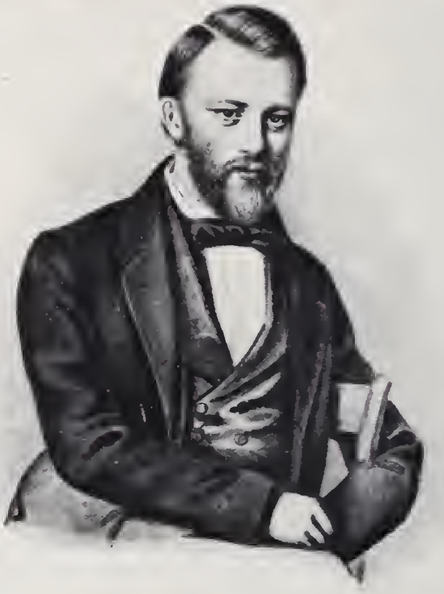

FIG. 2. Theodor Billroth in 1858 as assistant to Bernhard von Langenbeck in Berlin, at the beginning of his career.

During the Berlin years, Billroth reduced his musical activities to a minimum. With the stern self-discipline that he considered essential for productive work, he laid down the foundation for his surgical and academic career. He invested his rare leisure hours into visits to the Berlin Opera, one of the great European houses and the site of his grandmother's success as a soprano. Otto Gottlieb-Billroth, the surgeon's son-in-law, wrote about that period, "He (Billroth) often said that in the life of a young person who intends to produce something respectable in science or in any other field there must be a few years during which he concentrates energetically and without distraction on the task which he intends to accomplish. For Billroth, those were the years in Berlin at Langenbeck's clinic. During those years, he told me later, he at times did not leave the hospital for several months in a row" (16).

In 1858 Billroth married Christel Michaelis, the daughter of the Berlin court physician Edgar Michaelis. Her dainty appearance, her delicate face with melancholic dark eyes, and her natural charm led him to call her Mignon, after Goethe's heroine. Billroth's son-in-law described her as a woman "with a mind of great lucidity that could reach the heights of acute skepticism" (17). Her critical judgment in literary matters and her originality of thought made her an indispensable consultant for Billroth the writer. Of their five children, one daughter and the only son died at an early age.

The Years in Zurich

Late in 1859 Billroth received an offer to join the Medical Faculty at the University of Zurich as a professor of surgery and the director of the Surgical Clinic. He held that position from Easter 1860 to late 1867. His work during those years earned him an international reputation. In 1863 he published *Die allgemeine chirurgische Pathologie und Therapie,* the first and for many years the most authoritative textbook of surgical pathology and therapy. The work went through nine editions and was translated into eight languages. Further editions appeared in cooperation with Alexander von Winiwarter. Together with Pitha, Billroth edited the *Handbuch der allgemeinen und speziellen Chirurgie* (1865), to which he contributed several sections. In addition, he published complete accounts of the case histories at his clinic under the title *Chirurgische Klinik. Zurich. 1860–67.* In contrast to the custom of the time, Billroth's reports dealt not merely with the successful operations; they contained full accounts of failures and fatalities, detailed analyses and statistics. Ernst von Bergmann later described those reports as "stern, precice, and honest" (18).

Billroth approached his new duties at Zurich with his customary comprehensiveness. Shortly after his arrival, he took a complete and thorough inventory of the physical facilities. His final report included matters as disparate as the paint on the walls, the collection of surgical instruments, the quarters for experimental animals, the facilities for physiologic research and experimental surgery, and the annual budget (19). The report resulted in the renovation of the existing facilities and in plans for new buildings. Billroth also initiated and substantially contributed to reforms of the medical curriculum. He later incorporated many of his ideas and experiences acquired during that time into two major pedagogic works, *Ueber das Lehren und Lernen der medizinischen Wissenschaften* (Vienna, 1876) and *Die Krankenpflege im Hause und im Hospitale* (Vienna, 1881).

Billroth immediately became involved in Zurich's musical life with all its problems and difficulties. During the decade preceding his arrival, the city had shown a remarkable musical vitality. Numerous celebrities had appeared in concert and opera performances under the auspices of the Allgemeine Musikgesellschaft, a music society which, since its foundation in 1812, had been the leading constituent of Zurich's musical life. Richard Wagner, who lived in Zurich between 1850 and 1858, had personally conducted some of his operas. Between 1851 and 1855, Wagner had also appeared in 22 concerts sponsored by the Society. When Billroth became associated with the Society, it was at a period of decline. For financial reasons it had been forced to dissolve its famous orchestra, and thereafter it had become increasingly somnolent. To a large extent, it was Billroth's enthusiastic concern for musical matters, combined with a sober and realistic approach to the financial dilemma, that rekindled the Society's vitality. In 1862, mainly as the result of Billroth's efforts, Theodor Kirchner was appointed director of the Society and conductor of its new orchestra. Friedrich Hegar, his successor in 1865, was likewise Billroth's choice. Kirchner, and to a still greater extent Hegar, reactivated the city's musical life, and once again raised it to the level of international prominence. Later, Hegar commented on Billroth's contribution to the Allgemeine Musikgesellschaft, "His sound ideas were often decisive and his originality rejuvenated the rather lethargic Society" (20). Hanslick described Billroth's contribution to Zurich's musical life as "crucial and revitalizing" (21).

Between 1861 and 1863, Billroth periodically wrote music reviews for the Neue Zuercher Zeitung, the city's leading newspaper which, up to that time, had rarely featured critical reviews. He wrote at least two reviews for the Allgemeine musikalische Zeitung of Leipzig, published on 30 March and 18 May 1864 (22). Usually signed with the letters "h" or "th," Billroth's contributions commanded attention for their comprehensiveness, perception and eloquence in praise as well as criticism. His reviews were rarely restricted to the technical aspects of a performance. He systematically placed each major musical work into its historical and social context, gauging its position within the framework of the composer's total creation, weighing its inner consistency, and critically evaluating its specific contribution. In Billroth's view, a great work of art combined the essential elements of a tradition in a novel manner and thus at once questioned, extended, and reaffirmed the tradition out of which it had grown.

Next to Bach, Billroth greatly admired the classic composers. He repeatedly emphasized Haydn's originality. As an example, he singled out the string quartet in B-flat major, evaluating it as a work of most profound musical thought, almost equal to that of Beethoven. He considered string quartets in general as the most perfect instrumental music, excelling in "unity of musical texture, clarity of musical ideas, and perfection in harmony" (23). He regarded Beethoven as the exponent of all music and considered Schubert the only composer capable of approaching Beethoven's depth without straying into bombastic superficiality. Perhaps influenced by his own lifelong preoccupation with Goethe, he was especially fond of Mendelssohn's setting of scenes from Goethe's Faust. "How dramatic! How passionate! How grandiosely beautiful! What a crescendo from beginning to end" (24). He considered the work so important that he wrote an extensive analysis, based on a letter by Goethe to the young Mendelssohn.

As did Schumann in his famous essay *Neue Bahnen,* Billroth regarded the young Brahms as a true innovator, an artist who "raised himself gradually and in an immense struggle from a period of storm and stress, in the true sense of the word, to the level of highest clarity and complete integrity" (25). But he was by no means given to unconditional adulation of his future friend. In his early newspaper reviews as well as his later abundant correspondence he remained one of the composer's most severe critics. In the D-major serenade, for example, he found "despite all effort no logical inner relationship between the themes." He criticized the first movement for its lack of originality. "It appears to us as if we had heard something very similar in certain Haydn symphonies" (26).

Billroth, by training a pianist, began to take viola lessons in order to participate in performances of string quartets. Within a short period, he mastered the new instrument sufficiently to play with musical celebrities like Kirchner, Jean Eschmann and Hegar during regular weekly chamber music gatherings held at his home. We know from his correspondence that he spent many hours at the piano, playing original pieces or his own transcriptions of symphonies and chamber music. During the season of 1863–64 he, on at least two occasions, was the guest conductor at concerts sponsored by the Allgemeine Musikgesellschaft, and he composed three trios, a string quartet and a piano quintet during that time (27).

The beginning of Billroth's famous friendship with Brahms, which was to last a lifetime, falls into the Zurich period. The exact date of their first encounter is uncertain. Though they may have met briefly at Basle in the summer of 1865, at a performance of Bach's St. Matthew Passion under Kirchner, it is generally assumed that they made their first personal acquaintance in late autumn of that year at Zurich (28). Brahms related his cordial reception at that city in a letter to Clara Schumann. In the same letter he casually and without perceptible interest mentions Theodor Billroth as one of the sponsors of a private Sunday morning concert in his honor (29).

Brahms was already well known, although by no means internationally famous. He had achieved recognition as a conductor, pianist and composer of chamber music and a piano concerto. He periodically concertized with Joseph Joachim, the renowned violinist, whom he had met in 1853, and who later was to become one of Billroth's closest friends. Brahms' major symphonic creations lay still ahead, and the work on his great German Requiem, though begun in 1857 after the death of Robert Schumann, was resumed only in 1865, the year of his mother's death.

After their first meeting, Billroth took the initiative in strengthening his acquaintance with Brahms, which proved a difficult task in view of the composer's harsh and abrupt manners and his suspicion toward strangers. Brahms' brusqueness, which largely reflected his shyness in public, may have been accentuated by Billroth's professional fame. Billroth, in turn, described a curious incident reflecting his own nervousness in the presence of the composer. During one of the chamber music evenings at Billroth's house, with Brahms' string sextet in G-major on the program, the composer arrived unexpectedly. At his sight, Billroth lost his composure. 'I wanted to play the second viola, he wrote to Luebke. I had rehearsed my part perfectly. Yet as I began to play I started trembling and I was overtaken by such fear and anxiety that I was not able to continue" (30). Seven years later, Brahms humorously recalled that event in his dedication of his string quartets opus 51, no. 1 and 2, to Billroth.

> "It is not merely my sincere feeling for you and your friendship that makes me place your name at the head of my first string quartets. I simply cannot help being amused when I visualize you as a violinist and 'sextet player'. You probably would welcome a collection of the most difficult variations for piano more cordially and consider them more suitable for your talents. It does not matter, you will have to put up with this dedication and with its little funny afterthought" (31).

Billroth's first years at Zurich counted among the happiest and most productive in his life. At last he possessed the long desired professional

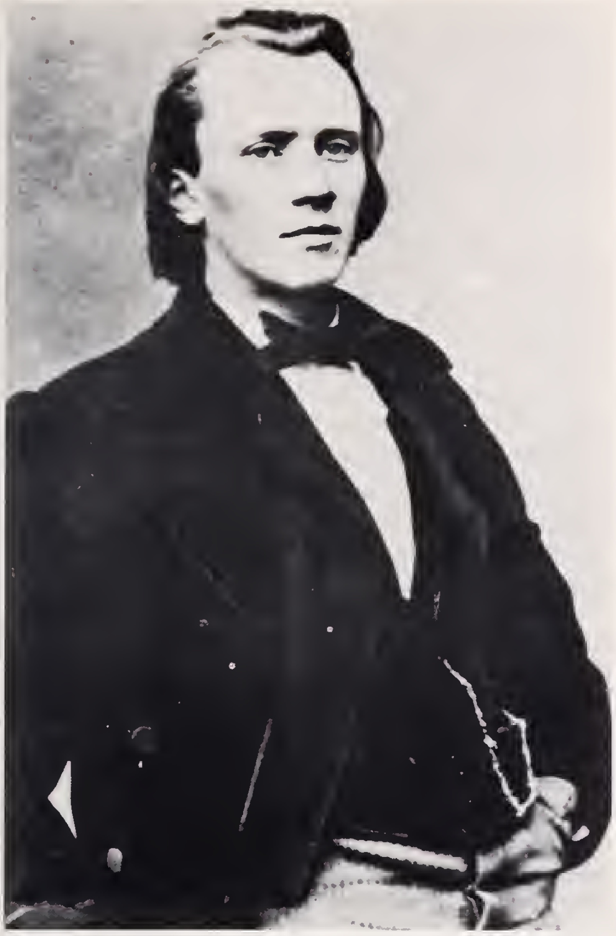

FIG. 3. Johannes Brahms, approximately at the time of the first meeting between Billroth and Brahms in 1865 at Zurich.

freedom. His fame spread steadily by means of his numerous publications. He attracted a number of talented students. Happily married, he maintained an active social life at his own house and at the home of his friends, to most of whom he related in the spirit of music. He frequented theater, concert and opera performances. He spent long hours conversing with friends at one or the other of his favorite taverns. He described that period to his friend His (1831–1904), the eminent anatomist and embryologist, in terms of glowing happiness. "As for myself, I am blessed beyond all merit, and if I were to die at this moment I would have been one of the happiest human beings. Everything is turning out for the best. Sometimes it frightens me" (32).

Yet despite this happiness, or perhaps because of it, there were growing overtones of restlessness and malaise. A state of tranquillity constituted a dissonance for a person who considered himself first and foremost a pioneer engaged in the task of paving the way for others. Like Goethe's Faust, Billroth regarded a life without perpetual striving an unfulfilled existence. In a letter to Hanslick, he noted that he had never been capable of harvesting the fruit of his labors in comfort (33). Thus it is not surprising that soon he should feel oppressed by a certain stagnancy inherent in his success at Zurich. Within less than a year after he wrote the above letter to His, the tenor of his correspondence had changed considerably. "I have achieved everything a surgeon can achieve," he wrote to Esmarch. "And that is a decisive misfortune for a man 37 years of age. If I do not get out quickly I shall soon totally degenerate in lethargy" (34). A few weeks later, in a letter to Luebke, he characterized his existence even more morosely as a state of "dissonance and disgust with life." In the same letter, he expressed his horror when facing the prospect of a solidly secure bourgeois life. "You must think I am insane! To receive, at the age of 37, one of the highest salaries in the country, to have achieved everything that can be achieved would be considered the height of good fortune by most people. For me it is a pitiful misfortune" (35).

During this state of emotional listlessness, Billroth learned of the remote possibility of a call to Vienna, the great metropolis of medicine and music. "They want to offer the leading professorship of surgery to a Prussian, a heretic" (36), he exclaimed in open incredulity. But despite all skepticism, he could hardly conceal his excitement over the possibility, no matter how vague, of filling a key position of surgery in Austria as the successor to the late professor Schuh.

The thought of living in the Imperial Capital dominated much of his correspondence. "During my lifetime Vienna will always remain a very great and very merry city," he wrote to Eisner (37). A year earlier he had declared, "I have the compulsive notion that one day I shall work at one of the greatest centers in my field, at Vienna or Berlin! It's ridiculous" (38). When the first hurdle, his election by the Faculty, with 11 of 17 votes in his favor, had been successfully taken, he wrote to Luebke, "I feel my head spinning at the thought of working in cosmopolitan Vienna. I have always wished for something like that, but now I am almost afraid" (39).

The Medical Faculty justified its choice of Billroth, the foreigner, by emphasizing his credentials as

> "a professor of surgery by whom science will be advanced to the highest degree; who is renowned not only as a practicing surgeon but as an investigator in physiology and pathologic anatomy; a man who already has excelled as a surgeon but who, nevertheless, is still young and therefore capable of combining successfully the latest achievements

> in surgery with those in physiology and pathologic anatomy; a man who is qualified to lay the foundations for a school of surgery at Vienna that will contribute to the well being of the country" (40).

Two months after his nomination by the Faculty, Billroth received three separate telegrams notifying him of his appointment by the Emperor, on May 12th, 1867, as professor of surgery of the Second Surgical Clinic at the University of Vienna.

With a unique blend of irony and sincerity he wrote to Luebke, "Indeed it strikes me like a plot of a novel that I should have been appointed Royal and Imperial professor at the first Surgical Clinic and the first Director of the Surgical Institute, appointed by His Apostolic Majesty, the Emperor of Austria, I, a man 38 years of age, who feels so much like a greenhorn that he is struck by fear and trembling at that thought. Please note the influence of the grassy green hill" (41). That last remark remains altogether cryptic when read at face value. Billroth, who was not much older than many of his assistants, was understandably tense about his key responsibilities at one of the world's great medical centers. At the same time he satirized his nervousness by expressing it in the alliterative style so dear to the Germanic heroes of Richard Wagner and so odious to Billroth himself. (The original reads, ". . . dass ihn bei diesem Gedanken fast ein Grausen ergreift.")

Wagner had resided at the country home of Otto Wesendonck, located on a green hill at the outskirts of Zurich. At the time of Billroth's letter, that hill had become a symbol for the whole spectrum of feelings generated by Wagner, ranging from unconditional adulation to passionate hatred. Billroth thought this sketchy allusion to a bit of musical information sufficient to catalyze a quite specific train of thought in Luebke. This is but one of the numerous examples from his writings to illustrate how strongly and idiomatically he communicated along the lines of music in relating to his friends.

Following his appointment, Billroth spent four turbulent days at the Austrian Capital to gauge the sites of his future activities. He summarized his impressions in a letter to Luebke, "This time I again found the city extremely congenial. The people are merry and carefree. One works moderately and enjoys life greatly." In the same letter, written from Zurich, he noted, "At Vienna I saw Brahms every day" (42).

Vienna

On August 20, 1867, Billroth began his work at Vienna. On October 11, he delivered his first lecture, "An Introduction to General Surgery." Billroth's enthusiasm for Vienna from a distance was quickly dampened by the realities of everyday life. By nationality, age and ideas he found himself an outsider among the conservative Medical Faculty. "Most of my colleagues are over 60, none is younger than 55," he complained to Luebke (43). Many of his proposals for constructive changes were viewed as a young man's querulous attempts to disturb the state of peace and harmony. His requests in committees were voted down as a matter of routine. Even plans for improvements in his own clinic met with resistance. "It took me three months to arrange the surgical amphitheater according to my needs," he wrote, and added sarcastically, "perseverance and patience are essential and effective at this place because you rarely find them among the Viennese" (44). He was especially appalled by the rigid standards of education, with requirements reflecting whim rather than pedagogic principles. He severely criticized Vienna's medical scientists and educators for their narrow intellectual scope that expressed itself in a "petty hatred of the Berlin school of scientific thought" (45). On Christmas Eve he summed up his first four months in a letter to Luebke. "I have let my bomb explode and everyone rages against the impertinent intruder into their tranquil, philistine lives. I have been called here to fight, and there will be ample need for battles" (46).

The greatest source of disappointment, however, was the lack of intellectual versatility among his colleagues. Only a few months before his arrival at Vienna he had written, "I am immensely looking forward to finding there a group of people from whom I shall receive intellectual stimulation" (47). He instead found specialized skills and pedantic ambitions. "Here science is used by its practitioners as a costume which they put on to deliver lectures and to practice medicine, only to return afterwards to their country homes as trivial people" (48). About the bright stars on the Viennese medical horizon he commented, "Oppolzer, Skoda, Rokitanski are men close to seventy, so dull, one could die" (49). Somewhat understandably, his colleagues reacted a little less than cordially to Billroth's attitude. "At the moment I am disgusting in the opinion of all of them" (50).

But a year later, Billroth's wrath and his colleagues' antipathy had mollified. "In the meantime my adversaries have become silent. During the first semester I was exceptionally unlucky; . . . Now everything has turned into good fortune. Things have worked out far better than I deserve, and if I went to the theater, to concerts and to social gatherings less often, I would be able to work much more. But I have to intoxicate myself with the pleasures of life, or else I cannot accomplish any respectable work" (51). Subsequent letters express a steadily growing satisfaction with his life at Vienna.

The first two decades of Billroth's twenty-seven years at Vienna constituted the height of his medical and scientific career. Internationally famous as a surgeon, he traveled long distances to treat patients. He attracted some of the ablest minds as his students, many of whom subsequently honored his legacy with important contributions in their own right (52, 53). His name became associated with fundamental innovations in surgery and with extensive work in bacteriology, physiology, histology and surgical pathology (54–56).

With his immense professional activities progressing successfully, and with the acquisition of his own home, Billroth developed an increasing fondness of the Austrian capital, its amiable lifestyle, and the light-heartedness of its population. He took special pride in the musical background of his house at the Alserstrasse, acquired in 1874, which had been the property of Frank (1745–1821), a well known professor of medicine and the director of the Allgemeines Krankenhaus. "It will always remain most fascinating to me that Johann Peter Frank and Beethoven have been in my house, and that a similar event—let's be arrogant!—is being repeated almost a hundred years later in the same house between you and me," he wrote to Brahms and, in reference to his garden, he continued "Beethoven must have walked these paths; and isn't it possible that Haydn rehearsed in this house . . . ? Not unlikely. What a sublime triad: Haydn, Beethoven, Brahms" (57).

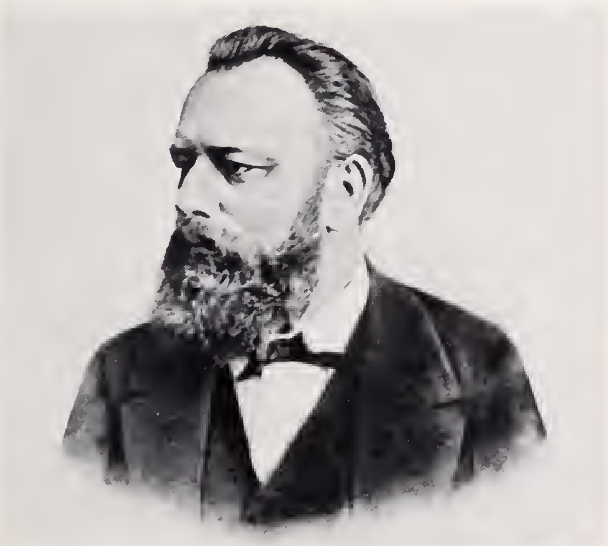

FIG. 4. Theodor Billroth at the age of 40, in Vienna, at the height of his illustrious career as a surgeon, scholar and educator.

Soon Billroth had so totally committed himself to Vienna that, in 1882, he, the Prussian, turned down the honoring offer to succeed Bernhard Langenbeck in Berlin. Eiselsberg, Billroth's assistant, later enthusiastically recalled the torch parade given by the medical students when they learned of his decision to decline the offer from Berlin (58).

Although Vienna counted an impressive number of luminaries among its inhabitants, Billroth's name gradually acquired a mythical aura with the man in the street. During his severe pneumonia in 1887, the popular fear for his health was so great that special bulletins were released periodically. When his predilection for a particular type of Viennese coffee cake became known, burghers and bakers alike flooded the house with gifts of that cake.

Perhaps to a larger extent than ever before, music was the backbone of Billroth's life at Vienna. He found the city's ancient musical tradition particularly fascinating. "Tradition," he wrote to Luebke, "is indeed a powerful force, especially in art. Tradition in art is nearly as important as heredity in nature" (59).

Vienna had been a musical center for nearly a thousand years. Initially restricted to monasteries, music rapidly diffused into the worldly sphere during the reign of the Babenbergs. At that time, the minnesingers held positions of great importance at court. Subsequently, the Hapsburgs acted as patrons of music, often with active participation in musical activities. They assembled musicians of fame from all parts of Europe, especially from Italy. Maximilian I, himself a trained musician, established a musical center which rivaled that of Florence under the Medicis. Ferdinand III wrote a number of religious works, and Leopold I composed an oratorio and 155 songs to be inserted into operas and oratorios. In the 17th century, Italian opera became firmly entrenched in Vienna, determining a tradition which, a century and a half later, led Mozart to writing many of his operas in Italian.

The Vienna of Billroth's day had retained its vigor as Europe's leading musical metropolis. The Imperial Opera was staffed with the most illustrious conductors and singers of the period. Its orchestra had long counted among the best when Otto Nicolai, in 1841, instituted a regular philharmonic concert series at which, besides himself, such famous conductors as Esser and Herbeck participated (60). The Gesellschaft der Musikfreunde, Vienna's leading musical society, founded in 1812 and still existing today, had counted Beethoven and Schubert among its members. It frequently collaborated with the renowned choral society, the Singverein der Gesellschaft der Musikfreunde, to include major choral works into its subscription series. The more recently founded chorus of the Singakademie was rapidly making a name for itself. The standards for chamber music, a genre especially close to Billroth, were set by the brilliant Hellmesberger Quartet. Billroth united that group periodically at his house to perform selections from the classical and contemporary repertoire. Much of Brahms' chamber music had its first performance on those occasions.

Next to Vienna's musical institutions Billroth was especially attracted by the Court Theater. As usual, he did not consider himself a mere consumer of art, separated from the stage by curtain and convention. After only a brief period at Vienna he wrote to Luebke, "My wife and I are literally at home at the Court Theater. I already know most of the actors personally" (61).

Vienna's musical life is richly and critically reflected in Billroth's abundant correspondence. Although he no longer wrote formal press reviews, the sections on music in his letters show the comprehensiveness, discernment and authority of a major music critic. His thoughts are all the more noteworthy in that they were synthesized in close communication with some of Vienna's most eminent musical personalities, like Brahms, Kalbeck and Joachim.

In addition to reviews of specific musical events, Billroth's writings, to a considerably larger extent than at Zurich, contained theoretical discussions of music in its historical and social framework. Central to his thinking was the question of value judgements in art. He evaluated contemporary composers, friends like Brahms as well as foes like Liszt or Wagner, in the light of music history and especially by the standards of the Viennese classical style. Yet he emphasized that ultimately the artist must stand judgement not merely as the bearer of a tradition but on the grounds of his own unique contribution to that tradition. "His uniqueness may encounter difficulty in being recognized if it does not fit into the mainstream of contemporary trends; but it certainly will be respected. And ultimately the important concern is whether that uniqueness expresses beauty, and expands and advances art. Only by that criterion can it be determined whether a given artist will hold a position in history, and of what caliber that position will be" (62).

During the six and one half years following his illness in 1887, which had led him to the brink of death, Billroth remained in poor health. Previously a person of seemingly boundless energy, he was forced to curb his manifold activities. Concomitant with frequent involuntary absences from his duties, certain manic depressive tendencies in his personality became intensified and his thoughts turned increasingly gloomy and introspective. An unmistakable spirit of pessimism emerged from much of his correspondence. Some of that pessimism diffused into his thoughts on music. "More than one thousand years fall between Sophocles and Goethe and, nevertheless, what unity of thought! . . . Mozart's Don Giovanni, Beethoven's symphonies will vanish, but Antigone, Hamlet, Faust will survive the human race" (63).

Significantly, Billroth's last major work, *Wer ist musikalisch?*, is a book about music. This fragmentary work, which occupied him to the last days of his life, reveals in simple and touching terms the essence of his love for music, which had inspired and unified his entire life. "A human being is capable of experiencing the highest form of bliss as a result of a simple sequence of melodies, a feeling of happiness beyond which none other exists and which, in certain respects, is purely ethereal" (64).

Shortly after those lines were written, on February 6th, 1894, Theodor Billroth succumbed to a heart attack. On February 9th, in the presence of an immense crowd, he was buried at Vienna's Central Cemetery.

Beyond Rationality

Music is the signature of Theodor Billroth's personality, the hallmark of his intellect both in its emotional and rational dimensions. It is likely that, at one point in his adolescence, he contemplated a career in music. Yet buoyed by the solid and orderly forces of a social background that provided for rational alternatives, he found a fruitful challenge in medicine. Although initially no more attracted to medicine than to jurisprudence or to any other field, he soon fostered that alternative with an enthusiastic dedication reminiscent of his dedication to music, while music became an endeavor of the leisure hours, albeit the essential activity to imbue him with strength in everyday life.

In addition to its rational components, however, Billroth's love for music shows a deeply emotional side, which ordinarily remained concealed behind a reserved and disciplined countenance, and which became further attenuated in the context of the written material available for analysis. On occasion, however, Billroth's writings offer insight into the intense exuberance and joy that lay at the base of his musical experience, for example, when he declared in reference to Schumann's incidental music to Byron's Manfred, "Grandiose poetry and grandiose music! One's senses become intoxicated. One dreams. One floats in lukewarm air without motion. The scene with the ghost of Astarte drives tears into my eyes each time I hear it. Indeed, at this very moment, while merely thinking about it, it makes me shiver. What sublime music" (65), or in his analysis of the dungeon scene in Fidelio,

> "It was an instinctive act of genius for Beethoven to write the great aria of Florestan, which opens the second act and which, toward the end, moves on visionary grounds almost beyond comprehension by the senses; and to have that aria followed by the sober, spoken voice, accompanied by music that paints trembling. Predominating are the spoken word and a dramatic situation which penetrates to the depth of our heart. One barely notices the music, though unconsciously one feels its power. A secco recitative would hardly have succeeded in capturing the intense realism of the situation, a realism produced by the contrast between Florestan's aria and the subsequent scene. The gravedigging duet begins, and the attention is shifted back to the music. And then comes the trio with its unbelievably beautiful, melodious and deeply moving motives in a gradual crescendo: it is so beautiful, one could perish! One can only weep, there are no words to express it (66).

Rationality and Enlightenment Philosophy

Billroth's rational view of the world unmistakably reflects the philosophy of Kant (67), who, in the *Critique of Pure Reason* (1781), proposed that man has within himself, and independent of his experience, the categories of space and time. Although man, according to Kant, is capable of assessing physical objects, such an assessment, by necessity, remains restricted to their outer appearances, which Kant called phenomena. The true property of matter, the "thing in itself", or the noumena in the Kantian terminology, are once and for all hidden from man's experience because he lacks the ability of analyzing his own *a priori* modalities.

Such a notion was revolutionary in the history of philosophy up to Kant's time. Yet Kant himself considered it a mere outgrowth of Enlightenment thought. Far from attempting to undermine the Enlightenment philosopher's belief in a universal harmony and in the spiritual nature of man, Kant continually strove toward strengthening both. His main query with the metaphysics of Leibniz and Wolff, the two exponents of German Enlightenment rationality was that the categorical imperative summons each individual to conduct himself in such a fashion that the rules underlying his conduct could become a universal moral law. Such an ethic, to which Billroth subscribed without Kant, a philosophy of metaphysics inevitably becomes speculative.

Billroth's confrontation with Kant's philosophy consisted essentially in accepting the whole while rejecting the parts; in subscribing to Kant's overall rationality while disregarding the philosopher's relentless inquiry into the limitations of man's reasoning; in viewing Kant's philosophy as dogma at a time when it had become a mere convention. In Billroth's day, the number of intellectuals who considered Kant's system a foundation upon which to build a harmonious existence had dwindled to a small minority, and Billroth was a representative of that minority who sought in Kant's teachings the philosophic matrix for their belief in an orderly and rational world. He did not share the anxiety and despair of the many who interpreted Kant's philosophy as conclusive proof of the futility inherent in any attempt to understand this world by reason; nor did he belong to the sizeable group of intellectuals, including many of the most astute thinkers of German Romanticism, who, in reaction to Kant, turned to the extraterrestrial world of fantasy and imagination in order to seek an answer to the meaning of existence. Instead, he molded his ethical standards according to Kant's categorical imperative.

One of the most fundamental statements of Enlightenment rationality was that the categorical imperative summons each individual to conduct himself in such a fashion that the rules underlying his conduct could become a universal moral law. Such an ethic, to which Billroth subscribed without hesitation, makes man's conduct essentially a matter of free will and individual initiative. It is therefore not surprising that Billroth remained reserved with regard to any collective system, whether political or philosophic, that demanded fundamental social reforms. For example, he showed little sympathy for Ferdinand Lassalle, the Social Democrat and leading organizer of the first German political workers' party, and Marx and Engels remained alien to him (68).

The Educator

Billroth the pragmatist translated his belief in the perfectibility of man and his world into concrete terms. Improving mankind for him was synonymous with educating man, a tenet essential to

Enlightenment philosophy. Billroth began his career as an educator in Berlin, concomitant with his residency in surgery. Both Langenbeck and von Graefe emphasized the young man's teaching ability (69). In later years, when an overwhelming work load as a scientific investigator, writer, and medical practitioner with extensive professional traveling would have justified a reduction of his pedagogic activities, Billroth nevertheless considered his work as an educator in the classroom, laboratory and clinic and in personal consultation with students of primary importance. At the height of his career he wrote, "I regard it my duty, especially in my present position, to be concerned not only with my own work, but with the education of students. I do not regret the amount of time spent at that task" (70).

The reaction to Billroth's teaching on the part of his students, however, was frequently one of controversy. His lectures were subject to criticism for their difficulty, despite their clarity and conciseness. Billroth was a master of content more than of form. Adept at assimilating new concepts with alacrity, he would often presuppose similar capabilities even in beginning students. Later he realized this with regret. "In view of the limited ability to assimilate knowledge in the majority of our listeners, it is indeed a basic prerequisite that the presentation be rather slow and distinct. I myself have not always been able to force my temperament to do this, and I know well that my students at Zurich needed the first half of the semester to learn how to follow me" (71).

Billroth demanded an unusual degree of intellectual flexibility from his listeners. Though greatly suspicious of intellectual speculation, he nevertheless weighed alternatives and pointed to possibilities just as emphatically as he presented proven theories. His determined refusal to glorify the state of current medical knowledge and his absolute honesty in questioning the validity of certain conventional medical views and scientific dogmas did little to ingratiate him with an average audience. It therefore comes as no surprise that for many years E. Albert, the professor at the First Surgical Clinic, was the most popular teacher (72, 73).

Mikulicz described Billroth, the teacher, as follows:

> "His lectures were not schoolmasterly like those a student, especially during his early semesters, is accustomed to hearing; they were no speeches which, when copied, would furnish a review for examinations, as most students, unfortunately, expect their lectures to be. His school was one of medical thought, a school of observation and exploration which every physician, not merely the scientific investigator in the strict sense of the word, should have to experience" (74).

In relating to his students on a personal level, Billroth carried out his conviction that a good teacher should concern himself just as much with shaping personalities as with propagating knowledge. His advanced students were offered an early opportunity of responsibility and independence both at the operating table and in research. Their progress reports or drafts for publication were customarily answered by a written critique, succinct in both its laudatory and corrective remarks. In dealing with controversial scientific issues, Billroth would willingly accept opinions of his students that differed from his own, as long as they were based on a respectable intellectual foundation. For example, though himself skeptical about Lister's technique of antiseptic surgery, he nevertheless encouraged his assistants to explore the new method without regard to his own views (75).

Cognizant that education is a matter of human as well as professional concern, Billroth frequently invited students to his home. He was naturally attracted by those who, like Johann von Mikulicz, the future famous surgeon, showed an interest in music. In his eulogy, Mikulicz recalled the unforgettable evenings when he had been invited to Billroth's house for a concert by the Hellmesberger Quartet, frequently with a new work by Brahms on the program, often in the presence of the composer himself and with Billroth's participation as a performer (76).

As at Zurich, Billroth's educational activities at Vienna were not confined to the teaching of students. His persistent efforts concerning a broad spectrum of educational matters resulted in some half a dozen publications, including the book *Ueber das Lehren und Lernen der medizinischen Wissenschaften* (1876). In addition, he invested a good deal of time and energy into planning new classroom and hospital facilities. In the fundraising for his building projects, he frequently set an example with generous contributions out of his own pocket. The Rudolfinerhaus, a school for nurses with its own teaching hospital, as well as the building of the Austrian Medical Association with its educational facilities were almost entirely a product of his initiative and continued concern. After their completion, he drew up extensive plans for a new institute of surgery, which occupied him until his death.

Perhaps no single statement is better suited to illustrate both the human concern and the realistic attitude underlying Billroth's educational activities than the preface to his pedagogic work

The Care of the Sick in the Hospital and at Home. "One at times meets people who strongly distinguish between the unique properties of the heart and those of the mind. Yet genuine and lasting kindness of heart goes hand in hand with action guided by reason. It is my deepest conviction that our happiness is indelibly linked to the happiness of our fellow man and that we, in performing good deeds, merely improve ourselves and pursue our own happiness" (77).

The Roots of Social Conservatism

In view of Billroth's strong commitment to education as a means of improving the human condition, his rather irrational refusal of equal educational opportunities to the lower classes seems severely out of tune. His discriminatory attitude against the disadvantaged becomes unmistakable with regard to a sizeable number of poor medical students attracted to Vienna from the Hungarian provinces, most of them Jewish and most of them slow in assimilating the polished language and cosmopolitan manners of the Imperial Capital. In his book *On the Teaching and Learning of the Medical Sciences,* Billroth unequivocally polemicized against that segment of the student body.

His arguments were based on the inflexible belief that students from the lower classes were invariably destined to academic failure and that the primary motivation for studying medicine in such students was the desire to raise the social status of themselves and their families. Though not denying the possibility of extraordinary talent or even genius among the lower classes, he nevertheless considered an unintellectual upbringing in an average person a dangerous obstacle to academic success. At the same time he extolled the descendants of the middle classes as model students.

> "Their fathers have been university students. At home, in their family and among their relatives, the spirit of culture and the thirst for knowledge prevail. At the university, students from such families seek association with the groups from which they originated. The form and content of lectures find a soil which is well prepared in every way, a soil in which knowledge takes firm roots" (78).

He criticized opinions to the contrary as unrealistic. "There is a prevalent obsession that poor young men who aspire to a scientific career in spite of many obstacles must have an invincible urge toward higher things and must be unusually gifted" (79).

Billroth rightly demanded of a student a lively intellectual interest and a personal commitment as the basis for his medical studies. His attitude becomes objectionable, however, when he considers those attributes an automatic and exclusive concomitant of a bourgeois upbringing. Objection is in order not because he criticized sheer ambition and social climbing via medicine, but because he restricted those undesirable traits to the lower classes. "No profession, except perhaps the clergy, has been exploited as frequently as medicine by uneducated families who aim to climb into the upper classes on the shoulders of the younger generation" (80).

Conservative statements of that nature, applied to a predominantly Jewish segment of the population, are open to being interpreted as antisemitic. And indeed, Billroth's views elicited severe public criticism. An eloquent open letter by a well known Viennese jurist exemplifies the public controversy kindled by Billroth's discriminatory remarks. Its author contrasts Billroth's antisemitic statements with those of Richard Wagner, arguing that, while Wagner's furor about the biased public reception of his works, though unfortunately directed against the wrong segment of the population, was at least understandable, Billroth's antisemitic remarks were a product of pure prejudice (81).

However, a careful examination of Billroth's own social background suggests that his desire for social stability rather than ethnic or cultural prejudice lay at the base of his discriminatory remarks. Like so many German intellectuals of his time, Billroth was the son of a Lutheran minister. As such he had been born into a stable, metaphysically oriented social environment. In a conservative sphere of that sort, social change became virtually synonymous with social disintegration. Even Goethe had subscribed to such a view when he, a few decades earlier, declared that he would rather commit an injustice than tolerate social ferment.

That need for social stability, instilled in Billroth as a part of his Lutheran bourgeois heritage, became reinforced by his preoccupation with Enlightenment philosophy, with a system of thought which regarded this world as a manifestation of a universal orderliness, and which thus implicitly nullified the need for social reforms. Yet perhaps the most important factor contributing to his distrust of social change lies in the psychological complexity of his own upbringing. The oldest of five sons, Billroth had lost his father at the early age of five. His mother was a lively woman with a need for social diversion which, according to the restrictions of that period, became greatly limited by her status as a widow. A sensitive awareness of social status was further reinforced by the family's dependence on relatives. Though Billroth was not outspoken about such matters, the tenor of his correspondence reveals a consciousness of his early insecure existence amidst a solidly bourgeois society, and it probably is no accident that his difficulty in communicating with Brahms during the later years of their friendship related specifically to the composer's humble origin and to his loyalty toward his aging father, who allegedly had compelled his teenage son to the degrading existence of a piano player in the taverns of Hamburg's disreputable harbor district. Thus, it is very likely that his distrust of social change, psychologically generated in his childhood and intellectually rationalized by Enlightenment thought at a period when that thought had become shrouded in the mantle of conservatism, was at least partially responsible for his hostile remarks concerning the disadvantaged medical students. That those students were predominantly Jewish, though perhaps not altogether an accident, is not likely to be a major reason for Billroth's inflexibility. We instead may conclude that, in view of an otherwise complete absence of antisemitism in Billroth's writings as well as his personal life, his attitude stands criticism not primarily as a testimony of ethnic prejudice but of social conservatism. In this context, it is of interest that many of his closest friends, including Joseph Joachim, Karl Goldmark and Eduard Hanslick, were of Jewish origin. In a speech to the Austrian Parliament, Billroth commended Christian ministers as well as rabbis for their beneficial activities. In that speech he clearly extended equal recognition and social status to the three religions, Catholic, Protestant and Jewish (82).

Social conservatism is apparent in a number of other situations when Billroth failed to draw the practical conclusions from his intellectual insights. Thus, he deplored the detrimental effects of war while in the same breath justifying the Franco-Prussian War as an appropriate means for retaining the established social order (83). Similarly, he criticized the power of the stock exchange as an exploitation of the many for the gain of a few (84). Yet he did not make any practical effort to break that power. He considered financial security, as vested in the bourgeois classes, a key prerequisite for academic success, but he made no attempt to establish financial support for the socially and educationally underprivileged. To be sure, such a measure would have come a century ahead of its time. However, that Billroth did not even consider it as a theoretical possibility constitutes a debit in an otherwise remarkably concerned educator.

Goethe, Faust: Striving and Restlessness

Next to Enlightenment philosophy, Billroth was greatly influenced by Goethe, and particularly by Goethe's ideas concerning the transcendental value of activity. His lifelong preoccupation with Goethe is manifested in numerous quotations and in frequent references to the poet's literary figures as well as in comparisons of his own life to that of Goethe. A few years before his death he wrote to his cousin, Frau von Schmeling, "I am in the fortunate predicament of being able to unite the Dionysian and Apollonian nature within myself, like Goethe. Excuse the arrogance" (85).

Central to Goethe's thought, and one of the essential tenets of his major work, Faust, is the notion that the essence of existence lies in action and that there is a universal value underlying striving. For Goethe, activity was more than the sum of its physical components. Each act represented a particular manifestation of an absolute entity. No matter how insignificant, it revealed a transcendental force. In an early scene in Faust, for example, we encounter the doctor in a passionate struggle to define existence on the basis of his vast knowledge of nature and philosophy. Rejecting one concept after another, he finally realizes that it is activity which lies at the base of all existence. "At the beginning was the deed!", Faust exclaims.

Billroth's diversified activities reflect both Goethe's belief in the transcendental value of action and a Faustian restlessness, a refusal to succumb to the lethal forces of a routine life. Faust concluded a wager with the devil that he never would be lured into permanence and security. Billroth exhibited a similar horror of permanence, which expressed itself in his numerous travels, in his intellectual agitation, and in a lifestyle bordering the realm of the wreckless.

He routinely imposed upon himself a crushing work load, interrupted by a minimum of sleep. At one period at Zurich, for example, he was intensively occupied by writing his *Allgemeine Pathologie*. This task, like most of his literary work, was reserved for the late night hours. He nevertheless rose at six in order to hear Vischer's lectures on Faust, and he curtailed his sleep even further in order to find the time for viola lessions (86). After his illness in 1887, he barely reduced his work load. In 1890 he wrote to Brahms,

> "It was a busy, strenuous day, as usual. Everything according to schedule. I woke up early because of a wound on my finger, which had become infected. But I am used to that. It will heal soon. Then a constant ringing at the door. I hardly had time for breakfast with my wife and children. Messengers from hotels making appointments for medical checkups; the secretary of the Rudolfinerverein requesting a signature, etc. Finally, visits to private patients on whom I performed surgery yesterday. Then the hospital. Residents, surgeons, administators, everybody wants something. Damn it, it's getting late! Hurry! Into the lecture hall! Two hours of lectures and operations. Barely out of the operating room, and I am surrounded by people again. Finally home. Twenty minutes for eating. Then a difficult operation which lasts over two hours. Extreme care; finally success! All goes well. Quickly two glasses of cognac. At home. Six patients, some incurable: Lies! Lies as a consolation. Fifteen minutes for the five o'clock tea with my family. Again out, to visit four patients. Back home. Half an hour of rest. What a fortune! I finish Widmann's book. Then to the Renaissance concert. It gave me great joy. One and one half hours of tranquillity and soothing music. Then six unavoidable professional letters. And now: Enfin seul" (87).

Fond of social gatherings and a frequent guest at restaurants and taverns, Billroth placed few restaints upon his desire for gourmet food and generous allowances of alcohol and tobacco. Already at Berlin he realized, albeit with equanimity, the inevitable consequence of his fondness for the pleasures of the table. Shortly after being married he wrote, "I enjoy my domestic situation immensely and I am beginning to gain quite a bit of weight" (88). Later he remarked, "My firm resolution to continue the diet which I started at Carlsbad has become rather weak. When it comes to a fresh lobster I lose all willpower" (89).

As a physician well aware of the ill effects of his hedonist habits and his excess weight on his declining health, he nevertheless made an attempt at restricting himself only when it became absolutely necessary, and then only with a great deal of moaning. Thus he wrote to Czerny, in mid-1888, "Most unfortunately, my well being is tied down by heavy chains, namely, by moderation in eating, drinking and smoking. As a result I avoid all social activities because under those circumstances I easily fall back into my former comfortable existence and I become enraged the following day when I have gained two kilos" (90).

With patent mockery he commented to Brahms on the tranquil existence of the renowned scholar Jakob Grimm. "The greatest grief good Jakob with his meager demands on life ever suffered was moving a library at Cassel. Otherwise, no inner or outer tension. No Faustian yearning, therefore no Faustian arrogance and hubris. No inner passion. Everything smooth, uneventful, classical, as we imagine the existence of a Greek philosopher. Goethe, by contrast, had to struggle and fight, despite his favorable circumstances" (91).

In a letter to Luebke he expressed his restlessness in a tone of bitterness bordering on despair. "You realize how miserable a young man can be who is robust and healthy but already finished with life because he is lost in an impasse whence there is no escape. I am a person perpetually driven by an inner restlessness. No position in life, no single circumstance would ever render me permanently happy. In fact, the mere thought of permanence is spiritual suicide" (92).

Such a declaration from the pen of an eminent surgeon, scholar and writer approaching the zenith of his career becomes comprehensible only when interpreted in the context of his Faustian personality. Faust's striving represents Goethe's ingenious formula for infusing a higher meaning into the trite realities of everyday life without taking recourse to a metaphysical system. Faust is a character in search of salvation from a monotonous existence. Despite his intellectual activities he is haunted by the dullness of his days to a point of cursing life.

Billroth's life reveals a similar state of anguish. "It is ludicrous that my colleagues should admire my potential for work. Literary work and scientific research are my salvation! Without that anchor I would have shipwrecked a long time ago" (93). In a similar state of gloom he declared, "It becomes too much for me to drag myself through this world with that eternal feeling of duty and unceasing work" (94). Or, in a letter to Hanslick, "I have an infinite desire to escape. I cannot muster the energy for my tasks and duties for longer than two months. Then I have to be a human being again for several weeks. The older I become, the more it seems to me that our present-day concentration on one profession to fill a lifetime, and our excessive specialization are crippling to the mind, to be compared to a dwarf with one single giant arm" (95). Toward the end of his life he wrote to Brahms, "I am an old man, but the thought of any restriction is unbearable to me" (96). In younger years, he had repeatedly emphasized his unwillingness to undertake sacrifices for the sake of longevity. "So far as long life is concerned, it is a matter of opinion. If one has to fight for it by relinquishing pleasure and by living in mediocre intellectual and material circumstances, most people would gladly decline it" (97).

The thought of old age earned at the expense of pleasure was odious to a person who viewed existence essentially as a sensual process. "I have to extract pleasure from life to the fullest extent, or else I am unable to function" (98), he wrote to Esmarch as an explanation for his numerous visits to concerts, operas and plays, as well as restaurants and social events. During the first two months at Vienna, for example, at a period when the assimilation to a new environment with its taxing duties demanded the utmost of energy and time, he participated in numerous musical activities, in addition to various other types of entertainment. "Concerts: Five Rubinstein. Two Joachim-Brahms. Three Joachim solo. Two Hellmesberger Quartet. Five orchestra and chorus. Nineteen concerts in two months. What do you say to that?" (99). His correspondence abounds with references of visits to his favorite cafes and taverns, such as the famous Red Hedgehog at Vienna, usually in the company of close friends like Brahms and Hanslick. On those occasions it was not at all unusual for the conversation to stretch into the early morning hours.

But Billroth's hedonism by far transcended the trivial notion of pleasure. He possessed too fundamental a vitality and too profound an intelligence to experience life as a bland dichotomy of work, that is, hardship, and relaxation, enjoyment. Those acquainted with Bertolt Brecht's play Galileo will find a striking resemblance between Billroth's concept of pleasure and that of Galileo. Brecht said of Galileo, "It is important to realize that he does his work out of sensuality. It gives him pleasure to manipulate his instruments with elegance. A great part of his sensuality is of a spiritual nature" (100). The very same statement applies to Billroth. His hedonism must be sharply distinguished from the blunt epicureanism which randomly nurses on the pleasures of the moment. He loathed this brand of "carefree epicurean without ambition and idealism (101)." His sensuality was, in Brecht's words, of a spiritual nature. It permeated the whole spectrum of his activities, physical as well as intellectual, and it found its most exalted expression in his love of music.

Musical Friendships: Hanslick and Brahms

Billroth's intellectual and emotional bonds to music became manifest in his social activities and, above all, in his friendships. He knew many of Vienna's leading musical figures personally, and intense bonds linked him to two of the most notable representatives of 19th century music, Hanslick and Brahms.

Hanslick, the famous music critic, whom Billroth fondly called Hansi, had studied jurisprudence and philosophy at Prague and Vienna. In 1856 he was appointed instructor of esthetics and music history at the University of Vienna where, in 1870, he became a full professor. Like Billroth, he was honored with the title Hofrat, one of the greatest distinctions the Austrian emperor could bestow upon an individual. Equally distinguished as a music critic and an academician, Hanslick, in the opinion of many, compromised his keen musical judgement in his biased assessment of Wagner, who, in turn, immortalized him in the brilliant caricature of Beckmesser in Die Meistersinger.

Billroth did not meet Hanslick until 1867 at Vienna, but already in Zurich he had occupied himself intensively with his ideas about music, and especially with his major work, *Ueber das musiklisch Schoene* (102). Hanslick recalled their first meeting in his autobiography as follows.

> "After four months in Paris, I returned to my quiet study in Vienna, full of impressions of all kinds concerning the arts, social life, and nature; and enriched by fond personal memories. At that moment something occurred in my life which I hail and praise as an unexpected gift from destiny: Theodor Billroth! Not that I was in need of his beneficial surgical hand. He has deeply penetrated my heart without a knife! One morning he entered my study: A strong and robust man with a heavy brown beard, a beautifully shaped forehead and somewhat deeply placed blue eyes which radiated intelligence, joy of life, and kindness. What gave me the honor of such a distinguished visitor? I could only guess. It was the musician in Billroth. I had heard his name first when I visited Zurich during the summer of 1864. 'Too bad Billroth is not here,' professor Luebke had exclaimed. 'If only Billroth had not left town,' repeated the composer Theodor Kirchner, whom I had visited in the company of Luebke. My question concerning the interest the famous physician might take in me was answered with a description of Billroth's great love of music and his musical talent, which by far transcended that of dilettant. . . . What a fortune for Vienna as well as for Billroth himself that he exchanged the stuffy Zurich atmosphere for higher and more exhilarating spheres. Uniting in himself the features of an artist and a scientist; a scientific investigator without pedantry; a lucid personality, full of life's joy and enthusiasm, Billroth soon became closely attached to everything great, beautiful and worthwhile offered by Vienna." (103)

Behind Hanslick's ornamented style we discern a sincere dedication to Billroth. "There was always a friendly smile on his lips, resembling mild rays of sunshine. It is difficult to describe the magic which such a powerful, yet kind and harmoniously balanced person exerted on everyone who came in contact with him. In me he generated a deep and tender affection. . . . To find a friend, at the age of forty, with whom we do not merely discuss matters of common interest, but with whom we exchange sorrow and happiness in confidence, that is a rare gift from heaven" (104).

Billroth's correspondence reveals an equally cordial attachment to Hanslick (105). And yet, he was not given to unconditional admiration, even of his closest friends. On several occasions he expressed his regrets that Hanslick did not embody any dynamic contrasts in his personality and that his attitude toward life lacked the elements of Faustian striving (106).

Billroth and Hanslick counted among the few close friends of Johannes Brahms. Hanslick, who had met the young composer during the Rhenish music festival of 1854, observed in his autobiography, "Before long, Billroth had attracted the more talented musical minds of Vienna. He welcomed Goldmark, Nottebohm, Door, Epstein, Bruell, Robert Fuchs, Richard von Perger, Kalbeck and others with pleasure as his guests. The closer musical circle, however, was formed by the three of us: Billroth, Brahms and myself" (107).

It was Hanslick to whom Billroth entrusted his fragmentary work *Wer ist musikalisch?* in a note written three days before his death: "This manuscript is to be handed over to my dear friend Ed. Hanslick, who may decide what to do with it" (108). Hanslick published the book a year later.

An analysis of the famous Billroth-Brahms friendship is essentially limited to a body of correspondence which, although extensive, reflects personal elements only sporadically and often indirectly and in reference to previous conversations. Both Billroth and Brahms were of North German origin; they both lived as expatriates in Vienna; and despite their cultural assimilation, they never quite overcame a certain emotional estrangement from that city. Billroth repeatedly emphasized the importance of his North German Protestant heritage in the genesis of his personality and in the development of his musical preferences. On occasion, such as in his review of Beethoven's Missa Solemnis, he became overtly dogmatic about his Protestant background. "I heard it for the third time," he wrote to Luebke in 1875, "and I had studied it in advance. To me that music is much deader than the weakest passage of Bach or Handel. . . . It is dull and meaningless in its content. It is rigid and artificial music. Most people would agree, if they were only honest enough. . . . This is insipid music, especially for a Protestant ear which by tradition and upbringing has no means of poetic identification with it" (109). Billroth's statement that the Viennese would never understand Brahms' Requiem because it was 'too Protestant and Bachian' (110) indicates that he was quite conscious of the difference between the tradition represented by Brahms and himself as opposed to that of Vienna. It is evident that a common feeling of kinship by background and tradition, and of alienation by circumstance facilitated their relationship.

Yet whatever role their common background played in generating solidarity, it was music that ultimately welded their friendship. Over a long period Brahms published hardly anything without first soliciting Billroth's critical judgment. Much of his chamber music was first performed at Billroth's house, and one of the rare dedications Brahms ever made went to Billroth (111), who remarked that posterity would remember him more for his name at the head of the two string quartets opus 51 than for his own work. Later he wrote to Engelmann, his former student and at the time a professor of physiology at Utrecht, to whom Brahms had dedicated his third string quartet, opus 67, "I am afraid this dedication will keep our names alive longer than even the best of our own achievements,—not very complimentary for us, but beautiful for mankind which, in its healthy instinct, considers art more eternal than science. It is a lasting human precept that love weighs more heavily than respect" (112).

During Brahms' frequent absences from Vienna, Billroth wrote extensive letters, often including exciting reviews of musical events. Brahms reciprocated with an equally voluminous correspondence. His letters, though initially more reserved than those of Billroth, gradually acquired the warmth and sincerity of a deep friendship.

It is a mistake, however, to view the Brahms-Billroth friendship exclusively in a musical context and at the expense of its emotional components. Billroth united a number of illustrious musicians at his home. Yet none attracted him more genuinely than Brahms, and one may safely assume that Richard Wagner, despite his musical genius, could never have held a comparable place of esteem and affection.

While Billroth's objective interest in Brahms as one of the greatest composers of the time is easily explained in the light of his own love of music, his attraction to Brahms as a person is largely a matter of conjecture. He quite possibly admired in him the genius he himself did not possess. Convinced that his own work could be duplicated by others, Billroth saw in Brahms one of the few contemporaries capable of an authentic existence. Furthermore, it is likely that he was intensely attracted by the differences between Brahms and himself, differences which extended not merely to Brahms' creative years but to his adventurous life as a teenager in the shady regions of Hamburg, one of Europe's largest seaports.

Billroth's reaction to Brahms' unorthodox past, however, was distinctly ambivalent. Raised in the sheltered provincial atmosphere of a small town according to the solid standards of a bourgeois family, he was curiously fascinated by his friend's background. At the same time, Brahms' past constituted a major obstacle for Billroth in relating to his friend, especially during the later years (113).

Brahms, in turn, may well have seen in Billroth and his secure life of a family father and a successful professional man an antidote to his own vagrant existence. Years earlier the composer had longed to establish himself in his native Hamburg and applied for the position as conductor of the Philharmonic Orchestra of that city. He took his rejection, in 1863, as a major defeat, a traumatic experience that may well have intensified his isolation and contributed to the theme of loneliness which characterizes many of his vocal compositions. The melancholy of a forlorn wanderer, the longing for a stable home, the bitterness of an uprooted bachelor recur in his music and his correspondence. His mature years at Vienna, professionally the most stable period of his life, constituted a time of restlessness and longing during which he traveled more frequently and over longer distances than ever before.

Both Billroth and Brahms had chosen Vienna as a permanent residence at approximately the same time. A causal connection in their choice has been stipulated. In the opinion of one observer, Brahms followed Billroth to Vienna (114), while another states that Billroth's choice of that city came about more readily because his friend Brahms had moved there the previous year (115). It is true that musical considerations were of utmost importance to Billroth and that, already at Zurich, Brahms constituted one of his most unique and most personal links to music. However, Billroth's attitude and aspirations regarding his professional work, as expressed on numerous occasions, leave little doubt that his primary reason for moving to Vienna was based not on musical but on professional considerations. As for Brahms, the composer had established connections with Vienna long before his acquaintance with Billroth. His bonds with that city had become intensified after the rejection of his application for the position of music director in Hamburg.

Originally, Brahms had expressed an intense antipathy against Vienna. In 1854 he had asked Joachim, "Would you want to travel there like a missionary to the heathens in order to preach them the gospel?" (116). But seven years later, his attitude toward "the holy city of music" had mellowed. The northern stranger had been prepared for a tough struggle when, in November 1862, he had faced the Viennese audience with a concert of his own works. The event proved a resounding success, which undoubtedly intensified Brahms' attraction for Vienna. It is therefore likely that neither Billroth nor Brahms had considered the other's decision a primary factor for his own settlement at Vienna. One may safely assume, however, that their friendship, which had begun in 1865 at Zurich and which had strengthened despite the long distances between them, would not have developed to such a degree of intimacy without their common residence in the Austrian capital. In July 1873, the two adopted the "Du", the familiar form of address which testified outwardly to the closeness of their relationship. Of his eight trips to Italy, Brahms made four, including the first, in the company of Billroth (117). There is no better testimony to the depth of their friendship than their published correspondence, consisting of 331 letters, postcards and missives, edited by Otto Gottlieb-Billroth, the surgeon's son-in-law (16).

Wer ist Musikalisch?

The final manifestation of Billroth's lifelong preoccupation with music is his last book, *Wer ist musikalisch?*, which deals with musicality in man. The work is not a scholarly enterprise. It was neither conceived nor written as such. Fully aware that he was not subjecting himself to the stringent exigencies of a music scholar, Billroth humorously described it as the illegitimate child among his writings. In a letter to Hanslick he declared, "I do not pretend to have expressed anything new, as little as I insist that my opinion is always the right one or the only valid one" (118).

Hanslick knew how to read the book, namely, as the intellectual rendition of Billroth's deep love for music, as a document which aimed at kindling enthusiasm as well as critical thought in its readers, and not as a source of authoritative theories concerning the origin and development of musical forms. Brahms lacked this type of insight, and if there is fault in the composer's conduct toward his ailing friend, it lies in his harsh criticism of Billroth's endeavor to write a book about music. Brahms' friends and critics alike resented his brusque last letter about the book, which reached Billroth on his deathbed.

Guided by his belief that man's intellect functions as a totality and that artistic and scientific endeavor spring from an identical source, Billroth offers a synthetic view of music, compounded with the analytical tools of a scientist and imbued with the subjectivity of his musical-artistic experience. To what degree he succeeds remains a mute question because of the book's fragmentary character.

Billroth considered music an integral part of nature. He regarded musical rhythms as a phenomenon analogous to biological rhythms, such as respiration, heart beat, or locomotion. As an extension of those biological rhythms vested in him, early man invariably was led toward musical-rhythmic expression. Thus, musicality, despite biologically determined individual differences, constitutes an integral part of each individual's experience. Even in his speech, a person exhibits characteristic musical patterns. Billroth noted, for example, that he, for one, conversed in d-minor while changing to D-major during lectures and public addresses (119).

Wer ist musikalisch? reveals first and foremost Billroth's musical personality. Here, musical reality blends with musical imagination, objective facts become transformed by the forces of enthusiasm, and at the loftiest moments of musical awareness, the emotional and physical modalities fuse to a single totality, a force that was the mainspring and lifeblood of one of the greatest figures in the history of medicine and science of the 19th century.

> "The pure beauty of instrumental music can affect a musical person without any special association and with such a physical force that he is no longer able to speak. A constriction of the throat occurs, a type of sobbing, until tears relieve him from this almost painful state of sublime happiness. I have frequently observed such a state in myself, and at concerts I have been embarrassed, in view of my neighbors, about this emotional reaction which, on the other hand, I would not want to miss for anything" (120).

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Clinical Study of Netilmicin Therapy of Hospitalized Patients with Gram-negative Infections

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Abstract

Netilmicin was administered to 26 patients with presumed or proved infection. Infected material from these patients yielded 26 isolates of gram-negative bacteria, one of *Listeria monocytogenes*, and one microaerophilic Streptococcus. Four of six patients with bacteremia due to gram-negative bacteria were cured by netilmicin, and the patient with *Listeria monocytogenes* bacteremia also was cured. Twenty-three of the 26 isolates of gram-negative bacteria were inhibited by 6.25 μg/ml or less of netilmicin. The mean peak serum concentration of netilmicin on the first day of therapy was 9.95 ± 5.72 (SD) μg/ml. There were no severe adverse effects of netilmicin therapy in these patients; 46% of the patients developed increases of serum alkaline phosphatase. Netilmicin appears to be an effective and safe aminoglycoside for the treatment of serious infections due to gram-negative bacteria.

Introduction

The new semisynthetic aminocyclitol aminoglycoside, netilmicin, the 1-N-ethyl derivative of sisomicin, is active against a wide variety of gram-negative bacteria, including many strains that are resistant to gentamicin, sisomicin, tobramycin and amikacin (1, 2). Pharmacokinetic studies of netilmicin in healthy human volunteers showed that therapeutic concentrations for most susceptible gram-negative bacteria persisted in serum for six hours following intravenous administration of doses of 2 mg/kg (3). Animal studies indicate that netilmicin is both less nephrotoxic and ototoxic than gentamicin (4–6). We report the results of a clinical study of the therapeutic efficacy and toxicity of netilmicin in hospitalized patients seriously ill with infections caused by gram-negative bacteria.

Materials and Methods

Patient Population: Netilmicin was administered to 32 patients with 33 episodes of confirmed or suspected infection. We report on 26 patients who were treated for more than 24 hours. All patients were hospitalized at The Mount Sinai Medical Center. Informed consent was obtained from all patients in accordance with institutional policy. Netilmicin was the only antimicrobial agent active against gram-negative bacteria given to the patients with suspected or documented infection caused by gram-negative organisms except in the patients with severe infection caused by *Pseudomonas aeruginosa,* in which netilmicin often was administered in combination with carbenicillin or ticarcillin.

Drug Administration: Netilmicin was administered by intravenous infusion over a 30-minute period. Three patients could not tolerate intravenous administration and the drug was given intramuscularly. Netilmicin was given at a dosage of 1–2 mg/kg every eight hours to patients with normal renal function. In patients with impaired renal function, netilmicin was administered at a reduced dosage which was adjusted by following serum concentrations.

Bacteriologic Studies: Bacteria were cultured and identified by standard laboratory methods. The minimal inhibitory concentrations (MIC) and minimal bactericidal concentrations (MBC) of netilmicin for the clinical bacterial isolates were determined by the standard twofold tube dilution

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technique in Mueller-Hinton broth; an inoculum of 10^5 CFU was used. Synergy studies of netilmicin in combination with other antimicrobial agents were performed using the standard checkerboard titration technique. Serum concentrations of netilmicin were determined by the agar plate diffusion method using *Staphylococcus epidermidis* as the assay organism according to methods previously described (2).

Clinical Evaluation: All patients were examined daily and audiograms were obtained before, during, and after treatment whenever possible. Patients were observed for development of vestibular and auditory abnormalities. Serum creatinine concentrations were determined in each patient at least every third day and more frequently if indicated. Complete hemogram, SMA-18, and urinalysis was obtained prior to, during, and after completion of netilmicin therapy. Ototoxicity was defined as a decrease of 15 or more decibels in the range of 250–8,000 Hz. Nephrotoxicity was defined as a rise in serum creatinine concentration of 0.5 mg/dl or greater, or the presence of casts or proteinuria on urinalysis, in the absence of dehydration or other causes or renal failure.

Results

Clinical Profiles: Twenty-six patients were treated for 24 or more hours with netilmicin (Table I). There were 12 males and 14 females ranging in age from 19 to 81 years. There were 28 bacterial isolates obtained from these patients. More than one bacterial isolate was obtained in seven patients, and no bacteria were isolated from one patient. There were nine patients with bacteremia, four patients with pneumonia, two patients with sternal osteomyelitis, six patients with urinary tract infection, four patients with cellulitis, and one patient with intra-abdominal abcess. The duration of therapy ranged from one to 50 days. Seventeen patients were given another antimicrobial agent in addition to netilmicin. In most instances, this agent was not active against the clinical gram-negative isolate. Bacteriologic cure is defined as the complete elimination of the pathogenic bacterium, and bacteriologic failure as persistence of the pathogenic organism.

Patients with Bacteremia: Netilmicin was administered to nine patients with bacteremia; gram-negative bacteria were isolated from blood cultures in seven patients, one patient had bacteremia with *Listeria monocytogenes* and another with a microaerophilic streptococcus (Table IA). Four of the seven patients with gram-negative bacteremia given netilmicin showed bacteriologic cure. Three of the five patients expired because of their underlying disease. Six of seven gram-negative isolates were inhibited by less than 3.12 μg/ml of netilmicin. One patient with bacteremia caused by *Listeria monocytogenes* was successfully treated with netilmicin (MIC, 0.63 μg/ml).

Nonbacteremic Infections: Six of the patients treated with netilmicin had urinary tract infections (Table IB). Three of the four patients whose clinical course could be evaluated were cured of the infection.

Two patients with *Klebsiella pneumoniae* pulmonary infections were cured (Table IC). One of the two patients with sternal osteomyelitis due to *Pseudomonas aeruginosa* was cured with the combination of ticarcillin and netilmicin (Table ID). However, only one of four patients with cellulitis caused by gram-negative bacteria was cured with netilmicin (Table ID).

Serum Concentrations of Netilmicin: The peak and trough serum concentrations of netilmicin were determined on the first day of therapy (early) and three or more days after beginning netilmicin (late). There were no significant differences in the early and late values. The mean early peak concentration (±SD) of netilmicin was 9.95 ± 5.72 μg/ml; the mean late value was 9.78 ± 5.13 μg/ml (Figure 1A). The mean early trough serum concentration of netilmicin was 3.05 ± 3.48 μg/ml; the late mean trough serum concentration was 4.14 ± 4.16 μg/ml (Figure 1A). The peak and trough serum concentrations of netilmicin in patients with renal dysfunction did not differ significantly from those obtained in patients with normal renal function. The mean peak serum concentration in the patients with renal dysfunction was 13 ± 5.84 and the mean trough level was 5.43 ± 2.31 (Figure 1B).

Drug Toxicity: Although a rise in serum creatinine concentration was observed in seven patients, only one patient had definite drug-related decrease in renal function. In six of the patients, the elevation of serum creatinine was attributed to hypotension during surgery or to prior therapy with another aminoglycoside antimicrobial agent. Netilmicin was discontinued in three patients because of presumed nephrotoxicity.

Two patients complained of tinnitus and hearing loss on the first day and a third on the sixth day of netilmicin therapy; both had abnormal audiograms. Netilmicin was discontinued in these patients. One patient had an abnormal audiogram early during netilmicin therapy but the au-

TABLE I

Patients Treated with Netilmicin: Clinical Data

No.	Patient	Age/Sex	Site of Infection	Underlying Diseases	Bacterial Isolate
A. Bacteremias					
1.	M.P.	54/F	Acute cholecystitis	Alcoholism; cirrhosis	*E. coli*
2.	B.S.	36/M	Pneumonia	Metastatic carcinoma of lung	*Klebsiella pneumoniae*
3.	S.E.	34/F	Pyelonephritis	Hodgkins' disease, Stage IV	*Proteus mirabilis*
4.	M.P.	74/M	Infected abdominal aortic aneurysm	Diabetes mellitus	*Pseudomonas aeruginosa*
5.	L.B.	48/F		Chronic myelocytic leukemia; Coombs positive hemolytic anemia	*Listeria monocytogenes*
6.	M.S.	24/F		Aplastic anemia	*E. coli*
7.	F.L.	64/M		Renal failure; resection of aortic aneurysm; hemicolectomy	*Serratia marcescens; Pseudomonas aeruginosa*
8.	E.H.	75/F		Carcinoma of cervix; radiation cystitis	*Serratia marcescens*
9.	G.B.	35/M	Endocarditis on prosthetic valve	Drug addiction	Microaerophilic *Streptococcus*
B. Urinary Tract Infections					
10.	L.K.	40/F	Pyelonephritis	Renal carcinoma	*Serratia marcescens*
11.	E.H.	76/F	Chronic pyelonephritis	Carcinoma of cervix; ureteral obstruction	*Pseudomonas aeruginosa; Serratia marcescens*
12.	D.S.	69/F	?	Metastatic carcinoma of colon	*Serratia marcescens* *Pseudomonas aeruginosa*
13.	F.V.	78/F	?	Diabetes mellitus; femoral artery embolectomy	*Pseudomonas aeruginosa*
14.	J.M.	39/F	Pyelonephritis	Double renal collecting System	*E. coli*
15.	D.G.	76/F	?	Congestive heart failure	
C. Pneumonia					
16.	E.M.	63/F	Right lower lobe	Congestive heart failure	*Klebsiella pneumoniae*
17.	A.M.	19/M	Left lower lobe; empyema		*Klebsiella pneumoniae*
18.	J.O.	50/M	Left lower lobe	Metastatic adenocarcinoma of lung	*Pseudomonas aeruginosa; Proteus mirabilis*
19.	A.S.	33/M	Right upper lobe; right lower lobe	Cystic fibrosis	*Pseudomonas aeruginosa*
D. Miscellaneous and Soft Tissue Infections					
20.	J.M.	60/M	Sternal osteomyelitis	Coronary artery surgery	*Pseudomonas aeruginosa*
21.	L.F.	50/F	Sternal osteomyelitis	Diabetes mellitus	*Pseudomonas aeruginosa*
22.	J.H.	50/M	Cellulitis	Diabetes mellitus	*Proteus morgagni*
23.	D.M.	80/M	Cellulitis	Diabetes mellitus	*Pseudomonas aeruginosa; Proteus mirabilis*
24.	K.M.	81/M	Cellulitis	Diabetes mellitus	*Proteus mirabilis; Pseudomonas aeruginosa*
25.	E.S.	59/F	Cellulitis	Chronic lymphedema of right leg	*Serratia marcescens*
26.	L.P.	25/M	Abdominal abscess		*Klebsiella pneumoniae*

* S = susceptible
R = resistant

TABLE I—continued

No.	Netilmicin MIC (μg/ml)	Duration of Therapy (days)	Other Antibiotic Therapy	Susceptibilities (S;R)	Results		Complications
					Bacteriologic	Clinical	
A. Bacteremias							
1.	1.56	6	Clindamycin		Cure	Cure	? Hearing loss
2.	1.25	17	Clindamycin		Cure	Expired	
3.	1.56	4	Oxacillin		Cure	Expired	
4.	0.5	42	Carbenicillin	R (MIC, 50 μg/ml)	Cure	Expired	
5.	0.63	14	Oxacillin	R	Cure	Cure	
6.	3.12	1					Tinnitus; hearing loss
7.	1.56 1.56	3			Failure	Expired	
8.	12.5	12			Failure	Alive	
9.	>100.0	7	Penicillin		Failure	Alive	
B. Urinary Tract Infections							
10.	1.56	14			Cure	Cure	
11.	50 6.25	21	Carbenicillin	S	Relapse	Improved	? Hearing loss
12.	6.25 6.25	7	Penicillin	R	Cure	Improved	Superinfection with *Candida* sp.
13.	1.56	8			Cure	Cure	Urticaria
14.	3.1	2	Changed to ampicillin	S			
15.		9	Oxacillin cefazolin			Improved	
C. Pneumonia							
16.	0.78	10	Penicillin	R	Cure	Cure	
17.	1.56	23	Clindamycin	R	Cure	Cure	
18.	S (disc) S (disc)	2	Clindamycin	R R			Expired
19.	2.5 1.3 1.0	15	Oxacillin	R	Failure	Improved	
D. Miscellaneous and Soft Tissue Infections							
20.	2.5	47	Ticarcillin	S	Cure	Improved	
21.	1.56	50	Carbenicillin	R (MIC, 50 μg/ml)	Cure with relapse in 2 months	Improved	
22.	6.25	14	Clindamycin	R	Cure	Cure	
23.	1.56 3.12	5				Improved	
24.	6.25 12.5	6			Failure	Improved	? Ototoxicity
25.	1.56	7	Oxacillin	R	Recurred in 10 days	Improved	
26.	1.25	25	Clindamycin	R	Cure	Cure	

* S = susceptible
R = resistant

diogram improved despite continuation of netilmicin.

Nineteen patients had abnormal liver chemistries during netilmicin therapy. However, in only one patient were the liver chemistries normal at the onset of therapy. Twelve patients had an increase in the serum alkaline phosphatase, and seven patients also had increases of serum aminotransferases and bilirubin during netilmicin therapy. In seven patients, the abnormalities of liver chemistries could be related to other causes. The changes in liver chemistries were mild, and netilmicin was not discontinued in any patient. In four patients with abnormal liver chemistries when netilmicin therapy was initiated, the chemistries improved with therapy.

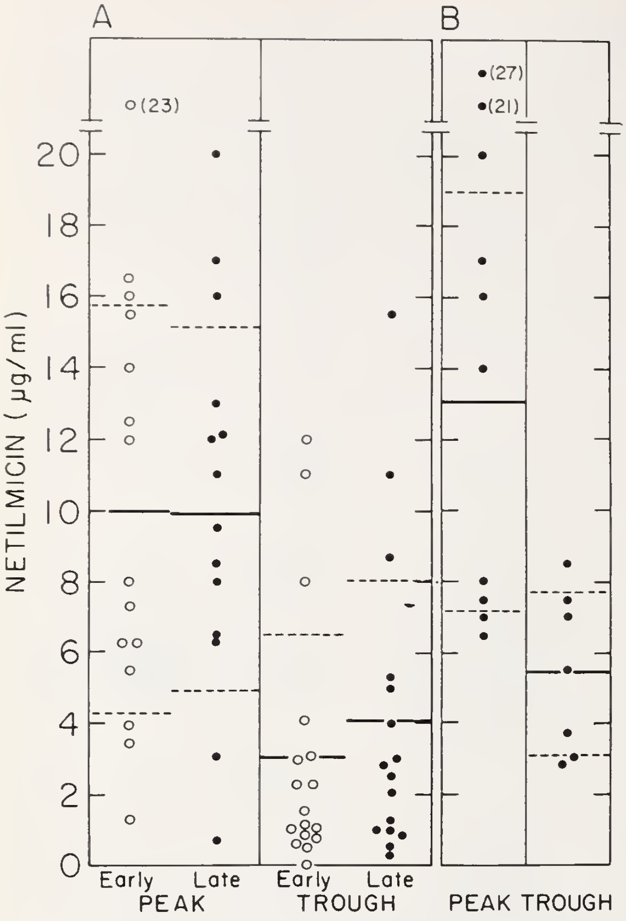

Fig. 1. Serum concentrations of netilmicin in patients with normal renal function (A) and in patients with renal dysfunction (B). The solid horizontal lines indicate the mean values and the broken lines the standard deviations.

One patient developed urticaria on the seventh day of netilmicin therapy, which cleared following discontinuation of the drug.

Discussion

In this study, netilmicin proved to be effective and safe in the therapy of patients with infections caused by susceptible gram-negative bacteria, confirming the previous reports of Klastersky et al (7), Panwalker et al (8) and Jahre et al (9). Only three of the 26 gram-negative isolates required more than 6.25 μg/ml of netilmicin for inhibition of growth. The therapeutic failures observed with netilmicin in this series of patients were caused either by resistant organisms or by foci of infection requiring surgery for ultimate cure.

There were no serious side effects observed caused by netilmicin. No patient developed severe hearing loss or renal failure. There was only one patient who developed skin rash. However, 46% of the patients had a rise in serum alkaline phosphatase. Panwalker et al (8) also reported increases in serum alkaline phosphatase in 43% of their patients treated with netilmicin.

There were no significant differences in the mean peak and trough serum concentrations of netilmicin early or late in therapy. However, although netilmicin was given in consistent dosage intravenously to the patients, there was great variability in the serum concentrations observed. Therefore, serum concentrations of netilmicin must be monitored during therapy, even in patients with normal renal function, to determine that sufficient concentrations are being achieved.

Infections caused by gram-negative bacteria continue to be an increasing cause of morbidity and mortality in hospitalized patients. These infections are often acquired in the hospital and the pathogenic organisms are more likely to be resistant to gentamicin or other aminoglycosides now in clinical use. Since cross-resistance among the aminoglycosides is not absolute, one must determine the susceptibility of the clinical isolate to all the aminoglycosides in order to determine the drug suitable for therapy. Netilmicin is a potentially useful aminoglycoside for the treatment of serious infections due to gram-negative bacteria.

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Subclinical Tropical Enteropathy in Angola: Peroral Jejunal Biopsies and Absorption Studies in Asymptomatic Healthy Men

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Abstract

Peroral jejunal biopsies and absorption studies were performed on 19 European and 13 African young, asymptomatic healthy men living in Angola. Under the dissecting microscope, leaves and ridges predominated in all. A predominance of fingers or a flat mucosa was not observed. The calculated average severity of the alterations was significantly greater in Africans ($P < 0.01$). Histologic studies revealed an abnormal jejunal morphology in all, characterized by villus dystrophy, vacuolization of epithelial cells, edema and infiltration of the lamina propria by lymphocytes and plasmocytes. Significant statistical differences in the occurrence of the alterations in the two groups were not detected. An apparent thickening of the basal membrane was observed only in four Africans. Elongated crypts were present in one European and one African. Results of mucosal measurements did not differ statistically in the two groups. Malabsorption of d-xylose was present in two Europeans (14.3%) and two Africans (15.4%), and malabsorption of glucose, in four Europeans (21.1%) and five Africans (38.5%). Malnutrition, anemia, or parasitic infections were excluded as etiologic factors.

Introduction

Asymptomatic, apparently healthy, people living in underdeveloped areas of the world have a high incidence of abnormalities of small bowel morphology and of malabsorption of one or more unrelated substances (1). These findings are characteristic of subclinical tropical enteropathy (STE) which has been described mainly in native born individuals and rarely in Europeans (2–4) and Americans (5, 6) living in the above mentioned areas.

Most reports come from countries where tropical sprue is endemic (2–20). STE, however, has also been described in areas where tropical sprue either does not exist or has rarely been observed (21–26). Reports from Africa are rare (22–25).

The purpose of this study is to establish whether STE occurs in Europeans and Africans living in Angola and to provide background data for investigation of tropical sprue and other malabsorption syndromes in that country.

Materials and Methods

Subjects Studied: All the subjects were males in military service. Nineteen were Caucasians from Portugal and thirteen, black native born Africans. The Europeans lived in Angola from three to twenty-five months (median time seventeen months). The age of the Europeans varied from 21 to 25 years and that of the Africans from 19 to 25 years. All were asymptomatic. Clinical examination was normal; there was no evidence of malnutrition, vitamin deficiencies, malabsorption, anemia, or hypoproteinemia. Hemoglobin, erythrocyte and leucocyte counts, erythrocyte sedimentation rate, blood urea nitrogen, serum glucose, albumin, iron, calcium, phosphorus, alkaline

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phosphatase, prothrombin time (Quick) by routine methods, and chest x-ray, were normal. Three stool samples were negative for ova and parasites by the Willis and Ritchie methods.

The procedures were explained to each subject and informed consent was obtained from all. For the purpose of the study, they were admitted to the University Hospital of Luanda.

Small Intestine Biopsies: Jejunal biopsies were obtained immediately distal to the ligament of Treitz using the Crosby capsule positioned under an image intensifier. Specimens were fixed in 10% formalin. The fixed specimens were blindly examined under a dissecting microscope. Dissecting microscopic appearance was graded from 1 to 5 according to the predominant villus pattern: Grade 1—fingers; 2—leaves; 3—ridges; 4—circumvolutions; 5—flat mucosa. The average severity was calculated for each group by multiplying the number of biopsies in each grade by x − 1, where x = grade − 1. The sum of values thus obtained was divided by the total number of biopsies.

Specimens were cut at 5μ and routinely stained with a variant of Masson's trichrome. Villus architecture, elongated crypts, alterations of epithelial cells of the villi, thickening of basal membrane, edema and infiltration of the lamina propria by lymphocytes, plasmocytes and eosinophils were evaluated. The average occurrence of the alterations was calculated by dividing the number of biopsies in which the alteration was present by the total number of biopsies. Infiltration of the lamina propria by lymphocytes, plasmocytes and eosinophils was graded + to ++++. A code average of the cellular infiltration was obtained for each group. The total number of biopsies was multiplied by grade +, less one, for plasmocytes and lymphocytes, and by grade +, for eosinophils. The sum of values obtained was divided in each group by the total number of biopsies.

Histologic sections were measured using a calibrated micrometer eyepiece. Total mucosal thickness (TMT) was assessed from the muscularis mucosae to the apex of the villi; villus height (VH), from the apex to the base; crypt height (CH), from the muscularis mucosae to the base of the villi; villus width (VW), at the widest part of the villi; epithelial surface cell height (EH), halfway up in the villi. At least eight readings were recorded for each specimen.

Absorption Studies: Microscopic examination of stools for fat was performed in all. Fecal fat excretion was estimated on a diet containing 70–100g of fat and expressed as a mean of three-day collection (27). D-xylose excretion was determined following a 25g oral dose and five-hour urine collection (28). Glucose tolerance tests were performed following a 50g oral dose. Serum glucose was estimated in venous blood at fasting and 30, 60 and 120 minutes after the glucose load, by the ferricyanide reduction method on the Technicon Auto-Analyzer (29).

Statistical Studies: For statistical studies, variance analysis by the Sheffé's method was used (30).

Results

Dissecting microscopy results showed that none of the biopsies had a predominance of fingers nor was flat. In European biopsies, there was a predominance of leaves, while in African biopsies, ridges predominated. Average severity was significantly greater in Africans ($P < 0.01$) (Table I).

Thirty-one biopsies were adequate for histologic study. An abnormal jejunal morphology was present in all (Fig. 1). Although normal villi were observed in some biopsies, architectural alterations were always present (Table II). Statistical analysis showed no differences between the two groups.

Elongated crypts were observed in one European and one African biopsy. The number of biopsies with irregularities of the disposition of cell nuclei and cytoplasmic vacuolization of these cells (Fig. 2), an apparent thickening of basal membrane and edema of the lamina propria are represented in Table III. Except for a greater occurrence of thickening of basal membrane in Africans ($P < 0.001$), the statistical analysis is not significant.

The average severity of the lamina propria infiltration by lymphocytes, plasmocytes and eosinophils is represented in Table IV. The differences between the two groups are not statistically significant.

TABLE I
Jejunal Dissecting Microscopy

Total Number of Individuals	Grade 1	Grade 2	Garde 3	Grade 4	Grade 5	Average Severity	
Europeans (19)	0	12	6	1	0	1.42	$P < 0.01$
Africans (13)	0	4	7	2	0	1.84	

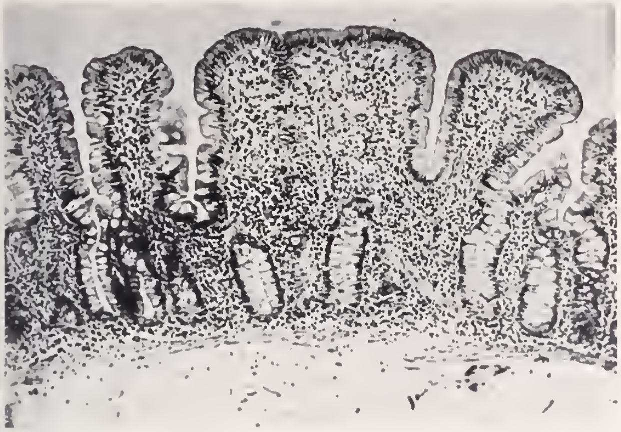

FIG. 1. Jejunal biopsy from an asymptomatic healthy African, showing bloated, stunted and fused villi. Increased cellular infiltration of the lamina propria classified ++ for lymphocytes and ++++ for plasmocytes. Masson's trichrome (×64)

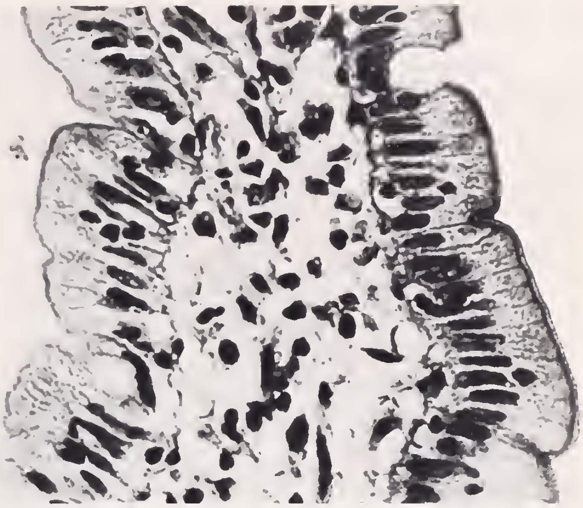

FIG. 2. Jejunal biopsy from an asymptomatic healthy African, showing normal columnar epithelium cells on the right side of the villus. On the left, the cytoplasm of the epithelial cells is vacuolated and the disposition of the nucleus is less regular. Masson's trichrome (×400)

TABLE II

Histologic Alterations

			Abnormal Villi				
Total Number of Individuals	Normal Villi		Fused	Branched	Bloated and Stunted	Clubbed	
Europeans (18)	7(a)	(0.389)(b)	8(0.440)	11(0.611)	15(0.833)	4(0.222)	N.S.
Africans (13)	5	(0.385)	8(0.620)	6(0.461)	12(0.923)	0(0.000)	

(a) Number of biopsies

(b) Average occurence of normal and abnormal villi

TABLE III

Histologic Abnormalities

Total Number of Individuals	Irregularities of Disposition of Epithelial Cell Nucleus		Cytoplasmic Vacuolization of Epithelial Cells	Thickening of Basal Membrane	Edema of Lamina Propria
Europeans (18)	17(a)	(0.944)(b)	17(0.944)	0(0.000)	11(0.647)
Africans (13)	12	(0.923)	8(0.615)	4(0.308)	6(0.333)

(a) Number of Biopsies

(b) Average occurence of abnormalities

TABLE IV

Average Severity of the Lamina Propria Infiltration by Lymphocytes, Plasmocytes and Eosinophils

	Lymphocytes	Plasmocytes	Eosinophils	
Europeans (18)	0.889	1.611	0.617	N.S.
Africans (13)	0.692	1.923	0.077	

Results of measurements of total mucosal thickness (TMT), villus height (VH), crypt height (CH), villus width (VW), and cell height of villus epithelium (EH) are indicated in Table V. There is no statistical difference between the two groups.

Microscopic examination of stools for fat did not reveal the presence of steatorrhea. Mean and standard deviation of fecal fat excretion, d-xylose excretion, fasting blood glucose and maximum rise in venous blood glucose over fasting levels are represented in Table VI.

In all the subjects, 24-hour stool fat was less than 6g per 24 hours. Excretion of d-xylose was less than 5g per 5 hours in two Europeans (14.3%) and two Africans (15.4%). All the individuals had normal fasting blood glucose. In four Europeans (21.1%) and five Africans (38.5%), maximum rises of blood glucose over fasting levels were under 25 mg/dl. Statistical analysis reveals no difference between the two groups.

Discussion

The predominance of leaves and ridges under the dissecting microscope is similar to that previously reported on STE. A predominant finger pattern, a rare finding in other studies (4, 9, 22, 26), was not observed by us. A flat mucosa, a rarer finding, is only reported in one of the biopsies studied by Cook et al (23), in Uganda.

Studies of celiac disease suggest that the patterns seen under the dissecting microscope may represent different degrees of severity of the same lesion (32). This makes the evaluation of the average severity of the alterations observed possible. Average severity was greater in Africans than in Europeans. Thomas et al (4), working in Rhodesia, reported a predominant leaf pattern in 62.5% of European biopsies, a figure similar to the 63.1% we obtained.

Studies on North Americans in Bangladesh (5) and on Europeans in Malasia (3) also revealed a predominant leaf pattern.

As for architectural changes of the villi, they are similar to those previously described. Elongated crypts, rarely observed in our cases, have seldom been described (7, 12, 13, 15), whereas cytoplasmic vacuolization of surface epithelium cells, frequently observed in our study, has been reported in only two previous studies on STE (7, 3). The thickening of basal membranes which we observed in African biopsies only, has rarely been described. A subbasal deposit of collagen, an amorphous substance and lipid globlets, have been observed under electron microscopy (18, 31).

As in other studies, observation of an increased infiltration of the lamina propria by mononuclear cells is constant. Plasmocytes have always been predominant. Although an increase in the lamina propria eosinophils has been previously described (2, 3, 12, 14), it was not found in the present study.

Our results and those of previous studies on measurements of the mucosa in STE are summarized in Table VII. African VH, CH, VW, and EH are greater than those observed in the only previous report from Africa (4). In Europeans, however, values for VH and EH are similar, whereas CH and VW are greater than those observed by Thomas et al (4), in Europeans living in Rhodesia. A similar group of healthy Norwegian

TABLE V

Measurements of the Mucosa (μ)

Number of Biopsies	TMT	VH	CH	VW	EH
Europeans (14)	571.0 ± 83.4[a]	357.9 ± 58.3	210.9 ± 41.0	159.9 ± 21.9	37.3 ± 4.1
Africans (13)	523.3 ± 86.1	307.3 ± 67.3	214.8 ± 36.2	171.1 ± 16.7	32.0 ± 8.3

[a] Standard Deviation; TMT—Total Mucosa Thickness; VH—Villus Height; CH—Crypt Height; VW—Villus Width; EH—Cell Height of Villus Epithelium

TABLE VI

Results of Absorption Studies

	Stool Fat g/24h		D-Xylose g/5h	Fasting Blood Glucose mg/dl	Maximum Rise of Blood Glucose mg/dl
Europeans	2.24 ± 1.08[a]	(19)[b]	7.31 ± 2.23 (14)	99.26 ± 11.19 (19)	45.20 ± 19.85 (19)
Africans	2.04 ± 0.61	(13)	7.34 ± 1.87 (13)	95.86 ± 8.55 (13)	33.85 ± 22.50 (13)

[a] Standard Deviation

[b] Number of Individuals Studied

TABLE VII

Measurements of the Mucosa (μ) in STE

	Country	TMT	VH	CH	VW	EH
Native born:						
	India(2)	—	440	251	127	—
	India(9)	430	—	120	—	38
	Thailand(11)	520	—	—	—	—
	Malaysia(3)	489	363	—	145	29
	Vietnam(14)	—	450	131	147	—
	Rhodesia(4)	—	293(a)	193	140	32
		—	302(b)	159	146	31
	Angola	571	357	210	159	37
Europeans:						
	Malaysia(3)	555	446	—	124	31
	Rhodesia(4)	—	311	150	143	31
	Angola	523	307	214	171	32

(a) Upper socioeconomic group

(b) Lower socioeconomic group TMT—Total Mucosal Thickness; VH—Villus Height; CH—Crypt Height; VW—Villus Width; EH—Cell Height of Villus Epithelium

young men was studied by Bürhol and Myrem (32) who found a greater TMT and VH, and lesser CH than those of the Europeans included in the present study.

Steatorrhea was observed in between 0 and 10.6% of native born individuals studied in Asia (8, 9, 11, 12, 35). In reports from Africa, however, this has never been documented. In the Europeans we studied, as well as in those investigated by Thomas et al (4), in Rhodesia, fecal fat excretion was normal. Steatorrhea, though, was observed in 18.1% of American Peace Corps Volunteers living in Pakistan (5).

D-xylose malabsorption was found in 12.5% to 57.8% of native born individuals studied in Asia (7, 8, 11–13, 35) and in 49% to 72.7% of those investigated in Central America (17, 18, 36). These figures vary from 7% to 39% in reports from Africa (24, 25, 37). Although d-xylose malabsorption was absent in Europeans studied by Thomas et al, in Rhodesia (4), it was observed in 14.3% of the Europeans we investigated. In American Peace Corps Volunteers living in Bangladesh, it was present in 3.3% of those protected from the "tropical milieu" and 39.5% of those nonprotected (3).

Fasting blood glucose levels are similar to those observed in India by Rajan et al (38), but lower than those observed in healthy people in South Africa (39) and England (40). The maximum elevation of blood glucose following the glucose load observed in India was 40.5 mg/dl (38), a value greater than that which we observed in Africans, but lower than that found in Europeans. For a lower normal range of 25 mg/dl, glucose malabsorption would be present in 21.1% of Europeans and 38.5% of Africans. The value for Europeans is similar to other previously reported all over the world, but greater for Africans (38). The difference between Europeans and Africans may suggest a greater severity of mucosal lesion in Africans. However, when intestinal absorption is the subject of study, the value of glucose tolerance tests is limited (41).

Conclusions

This study confirms the existence of STE in Europeans and Africans living in Angola. The etiology of mucosal lesions and malabsorption is unknown. In our subjects, malnutrition, anemia or parasitic infection may be excluded, but not subclinical tropical sprue. However, reports of this entity from Africa are scarce and for four years we looked for, but did not find, a single case in Angola.

The absence of small bowel alterations in foetus, (8, 10, 42) its presence in Europeans and Americans living in tropical areas, and the recovery in expatriates returning home from the tropics (43, 44), suggest the importance of environmental factors. Poor sanitary conditions in Angola, as well as in other underdeveloped countries, make infectious enteritis prevalent. The etiologic significance of these infections in STE must be investigated.

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QT Prolongation and Paroxysmal Ventricular Tachycardia Occurring during Fever Following Trimethoprim-sulfamethoxazole Administration

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Michael V. Herman, M.D.

Abstract

We report a patient, who on two separate occasions, developed QT prolongation and multiple episodes of ventricular tachycardia during fever following administration of trimethoprim-sulfamethoxazole. Ventricular pacing was effective in preventing the tachycardia. This case presents a possible new cause for QT prolongation and ventricular tachycardia and stresses the importance of checking the QT interval in acutely ill patients with ventricular arrhythmias. Drugs commonly prescribed for these arrhythmias—procaine amide, quinidine, and disopyramide—are contraindicated in long QT syndromes. Pacing may be the treatment of choice.

QT interval prolongation and ventricular tachycardia have been described following drug administration (quinidine, procaine amide, disopyramide, phenothiazines), electrolyte abnormalities (hypokalemia, hypocalcemia), cerebrovascular accidents, and myocardial infarction (1-7). We now report a patient who developed paroxysmal QT prolongation and ventricular tachycardia during two episodes of fever following trimethoprim-sulfamethoxazole administration.

Case Report

This 72-year-old man with "hairy cell" leukemia was admitted for evaluation of fever. He suffered from congestive heart failure treated with digitalis and diuretics. He had no history of hypertension, angina, myocardial infarction, ventricular arrhythmias, or syncope. There was no family history of sudden death. Physical examination on admission revealed a chronically ill man with temperature of 103.6 degrees, blood pressure 130/70 and a systolic ejection murmur at the left sternal border. The remainder of the physical examination was normal. Admission laboratory values included: Hgb-8 gm, WBC-8600, normal electrolytes and calcium, BUN-33. Electrocardiogram revealed normal sinus rhythm, normal intervals, and inferolateral ST-T changes. Chest x-ray showed moderate cardiomegaly. He was treated with a full course of cephamandole and tobramycin. All cultures from the time of admission were negative. After discontinuation of the antibiotics, he remained febrile (temperature 100–101 degrees). Extensive evaluation revealed no source of the fever.

Because of persistent unexplained low grade fever, on the 42nd hospital day, trimethoprim-sulfamethoxazole was initiated. One hour after a single dose, he developed shaking chills, a fever to 105 degrees, mild hypotension (BP systolic 80–90 mm Hg) and recurrent ventricular tachycardia. The QT_c interval which had previously been normal, was now 0.54 (Fig. 1A). Serum electrolytes, calcium, magnesium and arterial blood gases were normal. No further trimethoprim-sulfamethoxazole was administered. He was treated

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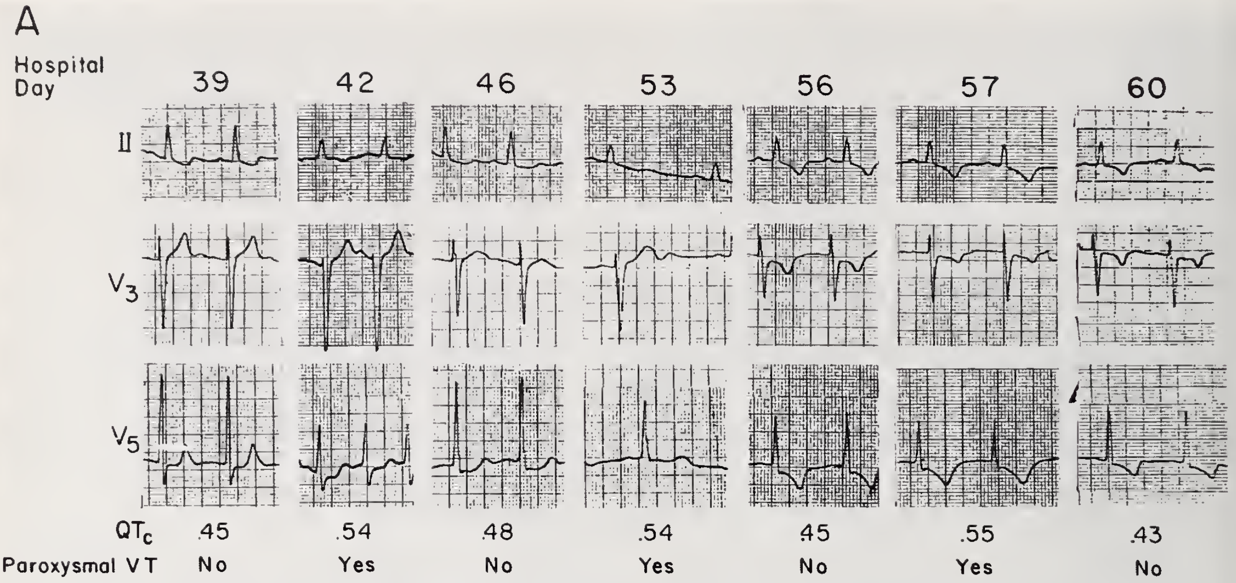

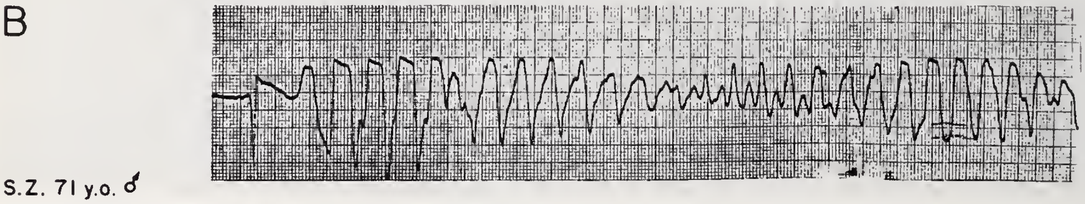

FIG. 1A Successive changes in the QT interval and relationship to tachycardia. Days 42, 53, and 57 demonstrate QT prolongation on the days that the tachycardia occurred. The patient received procaine amide from day 46 to day 53. He received single doses o trimethoprim-sulfamethoxazole on day 42 and day 57. Note that the QT interval was normal between episodes.

FIG. 1B A typical episode of the patient's ventricular tachycardia, demonstrating the torsades de pointes configuration.

with broad spectrum antibiotics, fluids as indicated by Swan-Ganz catheterization, and low doses of dopamine (<5 mg/kg/min). Despite lidocaine therapy (100 mg intravenous injection followed by 3 mg/min infusion), he had more than twenty episodes of ventricular tachycardia/fibrillation. Most of these episodes resolved spontaneously after 3–10 seconds, but he required defibrillation four times. Over the next three days, as his fever resolved and hemodynamics stabilized, the QT_c shortened (Fig. 1A) and the paroxysms of ventricular tachycardia subsided. All cultures were negative and the antibiotics were discontinued after five days.

Although the arrhythmia had subsided, because of its life-threatening nature, procaine amide 500 mg po was initiated 4 times a day. Monitoring revealed persistent isolated ventricular premature beats, and the procaine amide was gradually increased to 750 mg. po q3h. On the 53rd hospital day, paroxysmal ventricular tachycardia recurred. The QT_c was 0.54 (Fig. 1A) and the procaine amide level was 17.8 mcg/ml (therapeutic range 4–10 mcg/ml). Procaine amide was discontinued but hourly paroxysmal ventricular tachycardia persisted despite lidocaine, dilantin and bretyllium therapy. Temporary transvenous ventricular pacing at a rate of 110 beats per minute promptly suppressed the arrhythmia.

By the 56th hospital day, pacing had been discontinued, the QT_c had returned to normal (Fig. 1A), and the patient had no ventricular tachycardia. On the next day, however, trimethoprim-sulfamethoxazole was given for a urinary tract infection, and within hours, the patient developed shaking chills, fever to 104 degrees, systolic blood pressure of 90 to 100 mm of Hg, QT_c prolongation (Fig. 1A) and multiple runs of ventricular tachycardia morphologically similar to the previous episodes. The trimethoprim-sulfamethoxazole was discontinued. Broad spectrum antibiotics were instituted. The ventricular tachycardia was completely suppressed by ventricular pacing at a rate of 110 beats per minute. By the 60th hospital day, the fever resolved, and the QT_c returned to normal (Fig. 1A). Pacing was discontinued and there was no further ventricular tachycardia. Cultures were again negative and the antibiotics were stopped. Multiple determinations of cardiac enzymes during this period revealed no evidence of myocardial infarction.

The patient was subsequently found to harbor nasopharyngeal mucormycosis, and underwent amphotericin therapy, he suffered no further episodes of QT_c prolongation or ventricular tachycardia.

Discussion

This case presents a previously undescribed cause of QT prolongation and ventricular tachycardia. The patient developed QT interval prolongation and ventricular tachycardia on three separate occasions. Although one episode was clearly due to procaine amide toxicity, the other two episodes occurred in the absence of known precipitants of QT prolongation. Serum electrolytes were normal and the patient was not receiving any drugs known to prolong the QT interval. Both episodes occurred in the setting of fever and mild hypotension following trimethoprim-sulfamethoxazole administration. The temporal sequence and negative blood cultures suggest that the fever was related to drug reaction. Whether the QT prolongation and ventricular arrhythmias were secondary to the fever or directly related to the trimethoprim-sulfamethoxazole cannot be determined from this case.

One possible explanation for our observations is that the heightened adrenergic tone induced by fever with mild hypotension results, in susceptible patients, in sympathetic imbalance which then leads to QT prolongation and arrhythmias. While exogenous catecholamines were administered during the first episode, it is unlikely that they contributed to the arrhythmias, since they were not used during the second episode. Similar to other patients with secondary QT prolongation, our patient had evidence for underlying myocardial disease (7).

The recognition of QT prolongation, in this setting, has important therapeutic implications. Drugs commonly prescribed for ventricular irritability such as procaine amide, quinidine, and disopyramide are contraindicated (3, 4). Identification and removal of the precipitant is the first step in therapy of secondary long QT syndrome. Until the precipitant is effectively removed, Isoproterenol infusion or ventricular pacing may be the only means to prevent life-threatening arrhythmias (2, 4, 7). Increasing the heart rate may prevent arrhythmias by decreasing the dispersion of refractoriness in ventricular myocardium (8). Ventricular pacing, which completely suppressed the tachycardia in our patient, may be the therapy of choice.

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Retropharyngeal Hemorrhage and Acute Upper Airway Obstruction: A Complication of Catheterization of the Internal Jugular Vein

Manoon Lee, M.D. and Herbert W. Berger, M.D.

Abstract

We report a 68-year-old woman who developed retropharyngeal and upper mediastinal hemorrhage with partial upper airway obstruction following hypertonic glucose infusion into the right internal jugular vein. This is a previously unpublished complication of catheterization of the internal jugular vein.

Acute upper airway obstruction may result from hemorrhage into the retropharyngeal space due to a variety of causes. We report a patient who developed the previously unpublished complication of retropharyngeal and upper mediastinal hemorrhage with partial upper airway obstruction following hypertonic glucose infusion into the internal jugular vein.

Case Report

A 68-year-old diabetic woman was admitted to the hospital for hypoglycemic coma. In the emergency room a catheter was inserted percutaneously into the right internal jugular vein and 100 ml of 50 percent glucose in water was rapidly injected. Thirty minutes later she complained of difficulty breathing, pain in her throat, and inability to swallow.

On physical examination she appeared anxious. Vital signs were within normal limits. Examination of the oral cavity revealed anterior bulging of the posterior part of the pharynx. There was swelling of the soft tissues of the right side of her neck at the intravenous site. Stridor was not heard. The remainder of the physical examination was normal.

A lateral soft tissue x-ray film of the neck showed widening of the retropharyngeal space and narrowing of the upper airway above the larynx (Fig. 1). A chest roentgenogram revealed deviation of the trachea to the left and widening of superior mediastinum (Fig. 2). The coagulation time was within normal limits. Arterial blood gas studies were normal. She was treated supportively. Over the next several days she had marked symptomatic improvement. Repeat x-ray films of the neck and chest showed resolution of the previously described abnormalities. She was discharged on the sixth hospital day.

Discussion

Retropharyngeal and upper mediastinal hemorrhage with acute upper airway obstruction complicated hypertonic glucose infusion into the internal jugular vein in our patient. The internal jugular vein lies in a sheath of deep cervical fascia which is separated by a thin fascial slip from the retropharyngeal space. Perforation of the internal jugular vein and possibly the carotid artery caused leakage of blood and hypertonic glucose into the retropharyngeal space and led to severe swelling of this area. The upper mediastinal widening is explained by blood and fluid moving along the potential anatomic communications between the retropharyngeal space and the upper mediastinum.

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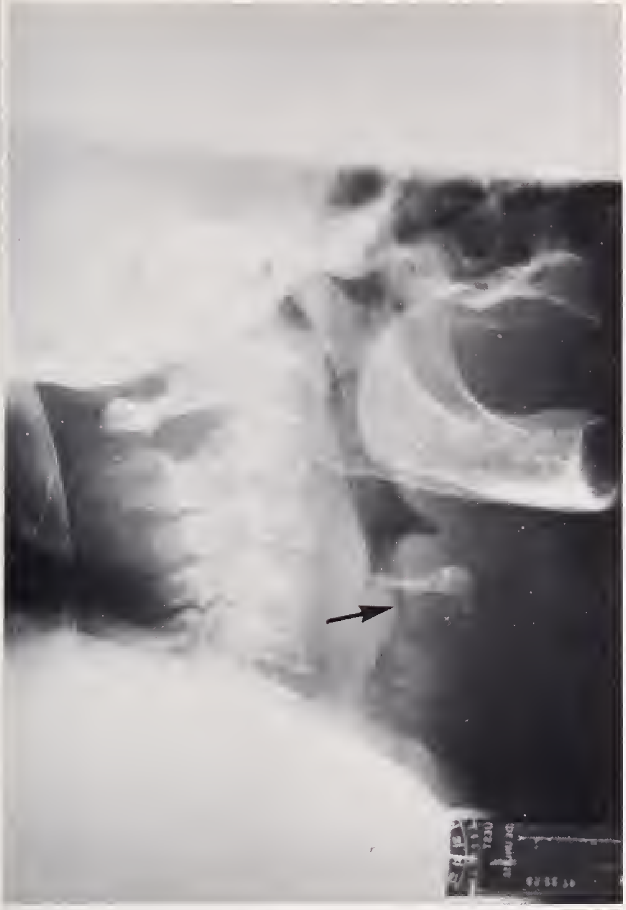

FIG. 1. Lateral soft tissue x-ray film of the neck showing widening of the retropharyngeal space and narrowing of the upper airway (arrow).

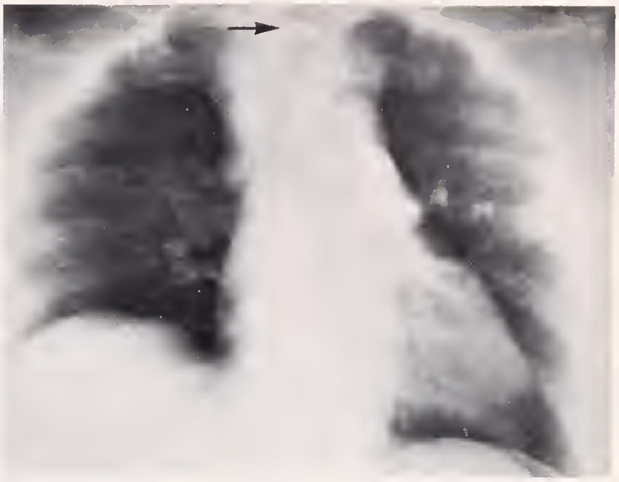

FIG. 2. Chest x-ray film showing the trachea deviated to the left (arrow) and widening of the superior mediastinum.

Retropharyngeal hemorrhage has been reported as a complication of neck surgery, external trauma, carotid angiography (1), transbrachial retrograde catheterization of the left ventricle (2), erosion of an artery secondary to infection, and anticoagulant therapy (3). McGoon et al (4) recently reviewed the complications of internal jugular venous catheterization. To our knowledge, retropharyngeal hemorrhage with acute upper airway obstruction following internal jugular insertion as described in our patient has not been previously reported. It is important that physicians be aware of this unusual complication.

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Barrett's Esophagitis: Unusual Features

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Barrett's esophagitis, first described in 1950, is an acquired disorder in which the stratified squamous lining of the distal esophagus is replaced by columnar epithelium. The lesion is related to chronic reflux esophagitis and as a result the characteristic roentgenographic appearance usually consists of an esophageal stricture, ulcer, and hiatal hernia (5, 7). We have recently encountered a patient with some unusual findings. The patient's clinical presentation was rather acute, her esophagus contained multiple large ulcerations and the length of the columnar epithelium was unusually long.

Case Report

A 70-year-old female was admitted because of an intertrochanteric fracture of the right femur. The patient had sustained a hip fracture seven years previously, and admitted to heavy smoking and ethanol abuse. She denied any history of heart ailment, diabetes or hypertension. Except for the recent fracture, the physical examination was unremarkable.

Skeletal traction in a Charnley boot was instituted. A few hours after admission she developed vomiting and intractable diarrhea. A provisional diagnosis of alcoholic gastritis was made for which she was treated. The fracture was eventually reduced in surgery and two days following the latter procedure, she began vomiting what looked like coffee-ground material. At this time, it was assumed that a stress ulcer was present and therapy for the ulcer was initiated. This consisted of Cimetidine and Mylanta as well as the placement of a nasogastric tube for secretion. The patient continued to have several episodes of hematemesis during the following days. Endoscopy was performed and revealed seven large bleeding ulcers within the esophagus. The squamocolumnar junction was noted at 20 cms and an hiatus hernia at 30–37 cms. Another ulcer, apparently not bleeding at the time, was also observed within the anterior wall of the duodenal bulb. The diagnosis of Barrett's esophagitis was suggested and documented by multiple biopsies and a technetium 99M pertechnate scan. The latter demonstrated irregularly and intensively increased activity along the entire length of the esophagus (Fig. 1). The esophagram showed a deep ulcer at the level of the carina (Fig. 2) and a second undermined large ulcer in the lower esophagus slightly above the herniated stomach (Fig. 3). The remaining ulcers were not identified on the contrast study. The bleeding was controlled after several days. However, the patient expired on the thirtieth day of hospitalization from a cause unrelated to her Barrett's esophagus. Autopsy was not performed.

Discussion

Despite the questionable etiology of the lesion, Barrett's esophagitis is presently considered to be an acquired lesion. Isolated remnants of columnar epithelium are still discovered in the esophagus in some patients as a result of embryologic development. However, the presence of a continuous sheath of columnar epithelium lining the esophagus probably represents the end stage of some form of reflux esophagitis. This concept is substantiated by observing the progressive rise within the esophagus of a stricture and adjacent columnar epithelium in many patients with this anomaly (7).

The presence of a hiatal hernia with coexisting reflux of gastric contents forms the necessary environment for this disorder to develop. Gastric reflux in some patients induces an esophagitis which results in destruction of the normal mucosal lining. Subsequent overgrowth of gastric mucosa then transpires. The latter regenerates approximately five times more rapidly than squamous mucosa and with passing years, gradually ascends the esophagus. As a result, the tran-

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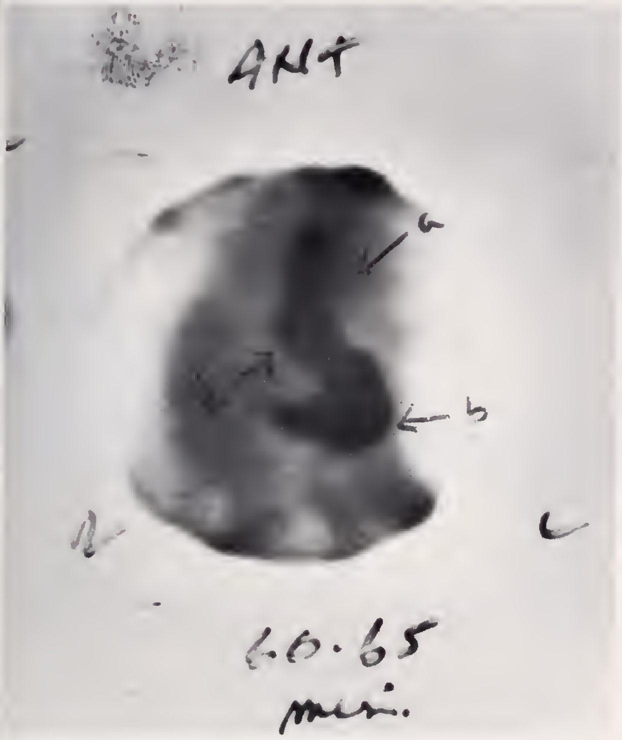

FIG. 1. The technetium scan shows activity along the entire length of the esophagus (arrow a). The stomach (arrow b) and the hiatus hernia (arrow c) are well seen.

sition between gastric and esophageal mucosa shifts cephalad and can be located anywhere along the esophagus. It has also been stipulated that the replacing epithelium may arise from congenitally remaining heterotopic nests of columnar epithelium which proliferate following stimulation by the refluxing gastric contents.

Three types of columnar epithelium in the lower esophagus have been described associated with this lesion—gastric fundus type, junctional-type and a specialized columnar epithelium. The specialized columnar epithelium is the most proximally located of the three. Histologic studies in most patients indicate the presence of parietal cells within the epithelium. Moreover, it has been shown that the columnar lined esophagus may secrete acid and pepsin (3).

Barrett's esophagus is usually discovered in middle or late life. The average age at the time of diagnosis is 57.5 years. The more common clinical presentation is related to chronic reflux and consists mostly of dysphagia, regurgitation, and heartburn. However, the diagnosis is most frequently considered when the complications of esophagitis arise, that is, stricture or ulceration (6).

Technetium^{99M} Pertechnitate shows selective concentration in gastric mucosa. It therefore helps substantiate the diagnosis by demonstrating abnormal concentration in the region of the esophagus. Although the mucosal lining resembles the stomach, motility studies nevertheless confirm that the underlying structure is still esophagus.

The uncomplicated case of Barrett's esophagus frequently manifests no characteristic radiographic features. The more typical findings, however, consist of a tapered or ring-like structure with or without associated ulcer formation (4). The stricture is always located at the squamous-columnar junction and is frequently discovered at the level of the aortic arch. A hiatus hernia is always present. Peptic ulcerations may develop anywhere along the esophagus from the cardia to the cricoid. These vary in appearance and it is important to recognize the distinction between the esophageal erosions that occur above the col-

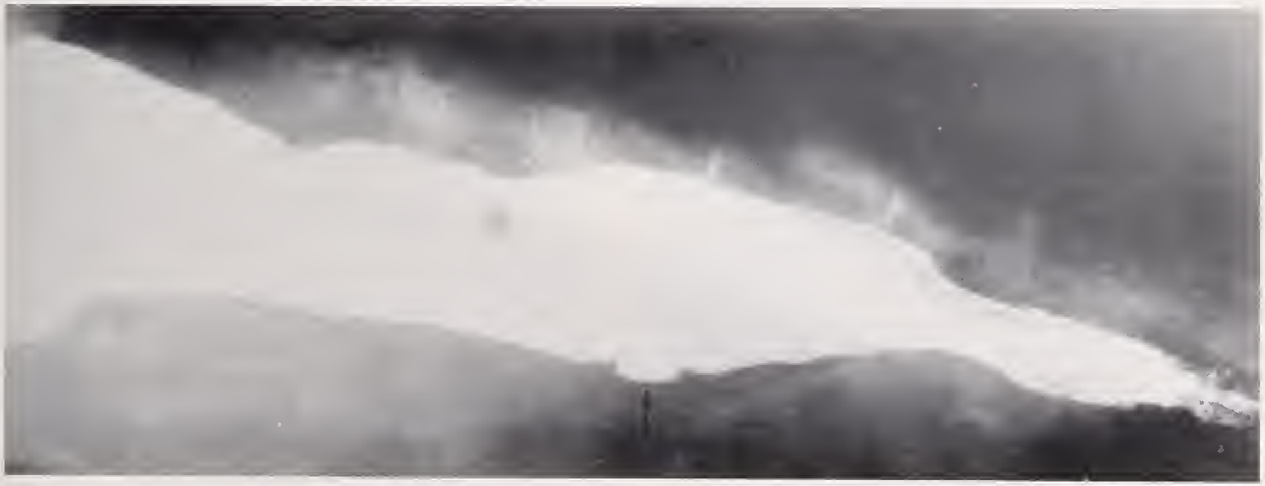

FIG. 2. A 1 cm ulcer (arrow) projects from the left side of the esophagus at the level of the left main bronchus. The esophagus is dilated and atonic and the mucosa slightly irregular.

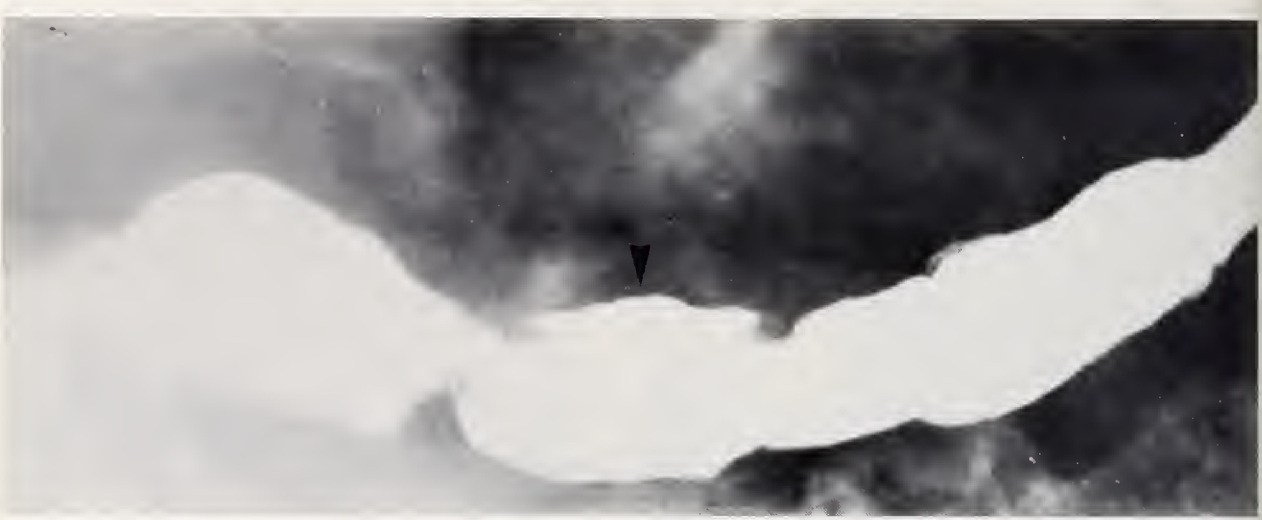

FIG. 3. A large 4 cm ulcer (arrow) is seen just above the hiatus hernia in the right anterior oblique projection.

umnar lined esophagus and the ulcerations that are found in the Barrett's esophagus. The latter are usually deep and penetrating. They differ pathologically and radiographically from the shallow erosions associated with reflux esophagitis. These erosions are encountered in the squamous epithelium and are identical to those associated with any hiatus hernia.

The complications of Barrett's esophagitis are hemorrhage perforation and carcinoma. Erosive esophagitis is a well known cause of slow gastrointestinal bleeding and may, at times, result in chronic blood loss. In our patient, the esophagitis was intense and resulted in the acute presentation of massive ulceration and hemorrhage. The incidence of coincident adeno-carcinoma is 10% (2). Therefore, columnar-lined esophagus should probably be considered a premalignant condition. Cases of Barrett's esophagus as a complication of scleroderma have also been described in the literature (1).

Cimetidine is the drug of choice for treatment of Barrett's ulcers. It leads to complete healing of the ulcer within a month (8).

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Squamous Cell Carcinoma Arising in Seborrheic Keratosis

JOHN KWITTKEN, M.D.

Seborrheic keratoses may undergo malignant transformation in the form of keratocarcinoma, basal cell carcinoma, or in situ carcinoma (1–4). Recently, I observed a deeply invasive squamous cell carcinoma that had developed from the base of a seborrheic keratosis.

Case Report

A 76-year-old Caucasian male noted the recent growth of a mole on his left arm. This had been present approximately 18 months. A pigmented verrucous skin plaque, 1.2 cm in maximum dimension, involved the lateral aspect of the left arm near the elbow, and resembled a cutaneous horn. Under local anesthesia, the lesion was excised and the base electrocoagulated.

Histologically, there was a papillomatous proliferation composed predominantly of uniform squamous and basaloid cells (Fig. 1). In some areas at the base of this verrucous lesion, the epithelial cells were considerably disorganized and pleomorphic, with nuclear hyperchromatism, mitotic activity, and dyskeratosis (Fig. 2). Focally, these anaplastic cells extended beyond the basement membrane zone relatively deep into the subjacent cutis in the form of anastomosing sheets, nests and cords. The surrounding stroma was focally edematous and infiltrated with collections of lymphocytes, histiocytes and neutrophils with a tendency towards localization about the small blood vessels. Foci of exocytosis associated with spongiosis of the verrucous lesion were present. The lesion was diagnosed as a squamous cell carcinoma arising from the base of an irritated seborrheic keratosis of the hyperkeratotic type. The surgical wound healed well with a slight scar and there was no recurrence.

Comment

Thus far, this represents the first documented case of an invasive squamous cell carcinoma developing from a seborrheic keratosis. As indicated in previous reports (2–4), there are probably a goodly number of diagnosed verrucous squamous

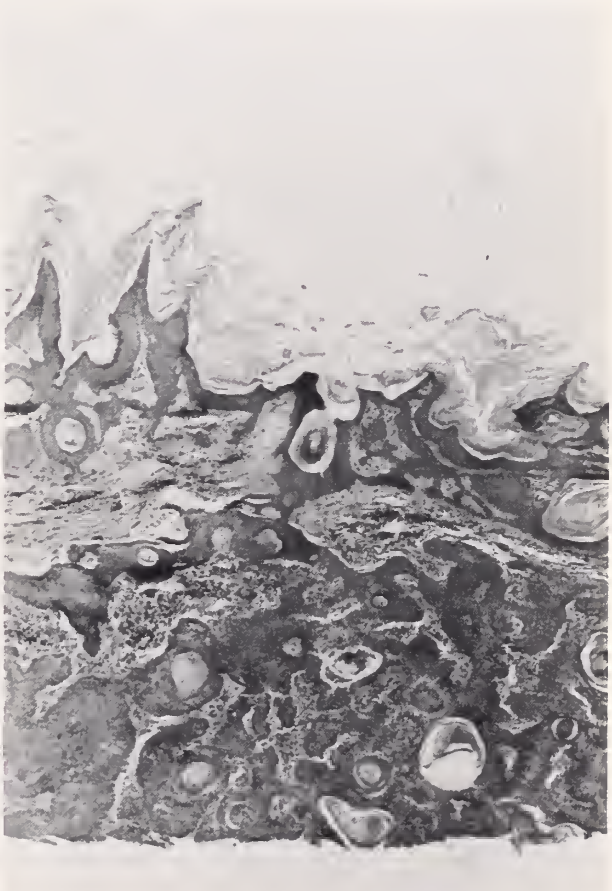

FIG. 1. Scanning view showing deeply invasive squamous cell carcinoma arising from base of hyperkeratotic seborrheic keratosis (H & E ×20).

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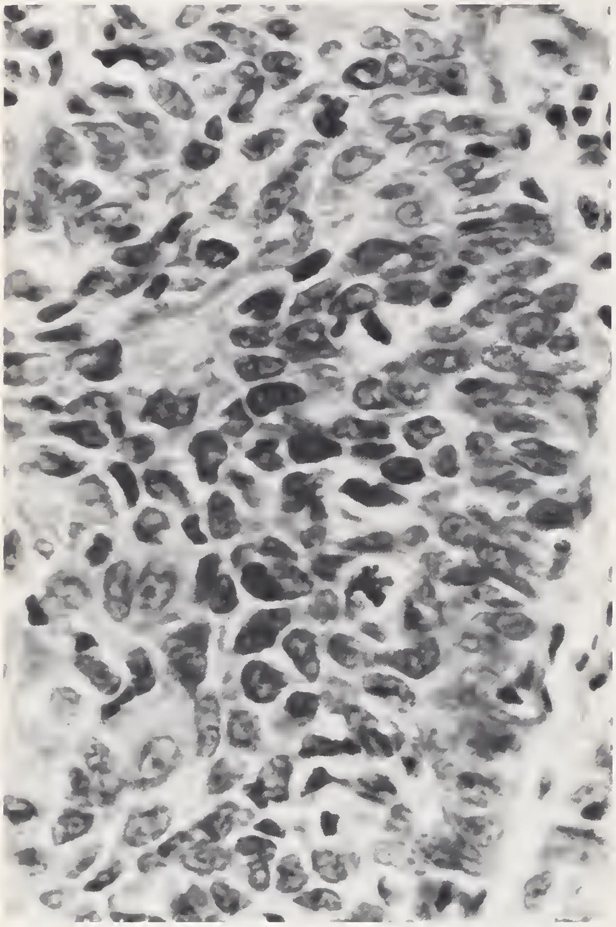

FIG. 2. High magnification of base of seborrheic keratosis demonstrating loss of polarity of epithelial cells associated with considerable nuclear hyperchromatism and pleomorphism and relatively frequent mitotic activity (H & E ×400).

cell carcinomas that most likely represent total malignant transformation of seborrheic keratoses with invasion. In the current case, recognition of the initial lesion was easy because most of it had not undergone malignant transformation. As previously emphasized (2, 3), clinically changing seborrheic keratoses should be biopsied since malignant transformation may occur, necessitating further therapy.

Summary

Invasive squamous cell carcinoma arising from the base of a seborrheic keratosis has been reported. This further emphasized the need for biopsy of clinically changing seborrheic keratoses, since more aggressive therapy may be indicated should a malignancy prove to be present.

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The Groin Flap: Report of a Case of Complications in the Donor Site

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The groin flap based on the superficial circumflex iliac arteriovenous system was described in 1972 by McGregor (1, 2). Since then, the flap has largely replaced the abdominal tube pedicle flap to resurface defects in both the upper part of the body as well as the lower limbs. This flap has greatly reduced the time required as well as the morbidity, while providing more skin which was usually softer and more flexible.

The major application of the groin flap has been its use in resurfacing defects of the hand. Both the dorsum and palm are easily covered, maintaining adequate movement of the wrist and fingers, because of the long pedicle of this flap. It has also been used for defects of the forearm as high as the elbow. When used as a transposition flap, the arc of rotation reaches defects of the abdominal wall, the opposite groin, vulva and perineum. With the advent of microsurgery, the scope of the groin flap has been widened immensely, providing a donor site of adequate tissue, with negligible cosmetic and functional deficits (3–6).

Complications from the use of groin flaps are few because of the generous blood supply of this flap. Complications usually result from poor planning of the flap or injury to the vascular pedicle. Doner site complications of a groin flap are even more rare, and have not been stressed in the literature. We now present such a case, exhibiting two separate complications in a donor area.

Case Report

A 45-year-old white male sustained a degloving injury to the palmar surface of his left hand on February 5, 1978. The defect was resurfaced by a left groin flap. The donor defect was covered with a split thickness skin graft. Six weeks postoperatively, he developed an infection in the donor site. This was assumed to be a soft tissue infection and he was treated with oral antibiotics. The infection appeared to resolve but three weeks after discharge he developed a draining sinus at the left iliac crest. Radiographic studies performed at that time revealed findings consistent with osteomyelitis of the ilium. He was again placed on oral antibiotics for several weeks but there was little clinical or radiologic improvement.

He was transferred to The Mount Sinai Hospital complaining of pain in the left hip on walking. He noted a burning sensation in the anterior thigh just below the incision. Physical examination on admission revealed the following vital signs: pulse 80/min, BP 130/80 mm Hg, and temperature 98.4° F orally. There was a small sinus tract, with minimal purulent drainage over the left iliac crest in a heavily scarred groin wound (Fig. 1). In addition, he was found to have no sensation in the distribution of the anterior branch of the lateral cutaneous nerve of the thigh. There was full range of motion of his left hip.

Laboratory studies done on admission revealed a hemoglobin of 13.8 gm%, white blood count of 12,200, and blood glucose of 89 mg%. Twelve channel blood tests showed a slightly elevated alkaline phosphatase of 91 mu/ml but was otherwise within normal limits. X-rays (Fig. 2) and a sinogram (Fig. 3) revealed extensive osteomyelitic changes of the ilium with the sinus tract extending along the anterior inferior iliac spine on the left. Multiple cultures of the drainage from the sinus grew Pseudomonas Aeuruginosa, sensivive to Colymycin, Gentamycin, Kamamycin, Tetracycline and Tobramycin.

On September 29, 1978, the patient was taken to the operating room, the old scar was completely excised and the sinus tract was removed down to the bone. There was extensive destruction of the

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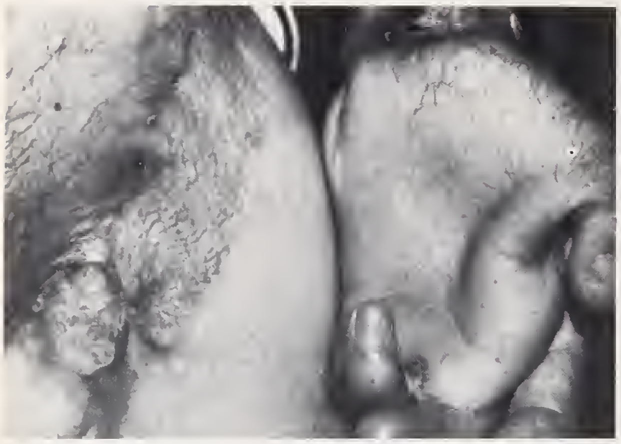

FIG. 1. The left groin flap was used to resurface L. hand. Note a sinus tract over the anterior superior iliac spine of the left groin.

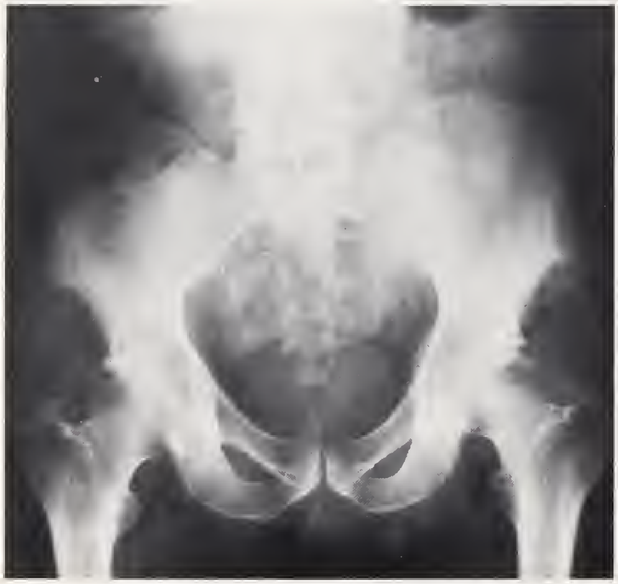

FIG. 2. The preoperative x-ray shows extensive periosteal reaction over the anterior superior iliac spine.

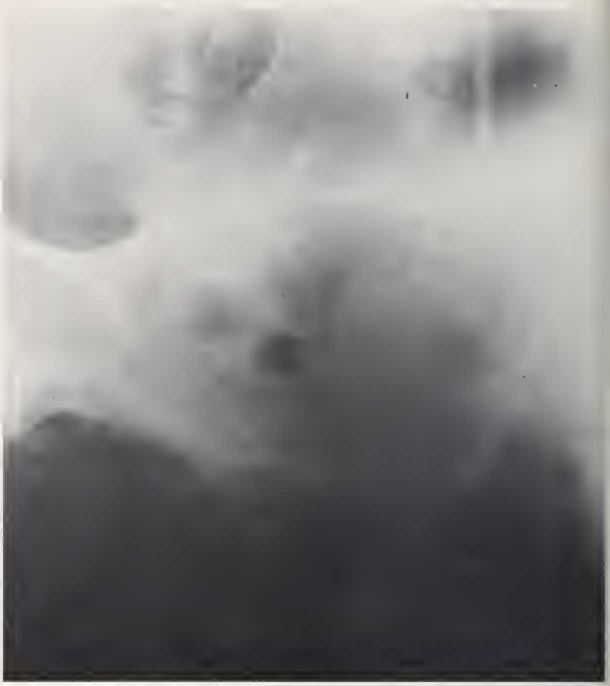

FIG. 3. The sinogram shows the sinus tract extending along the anterior inferior iliac spine.

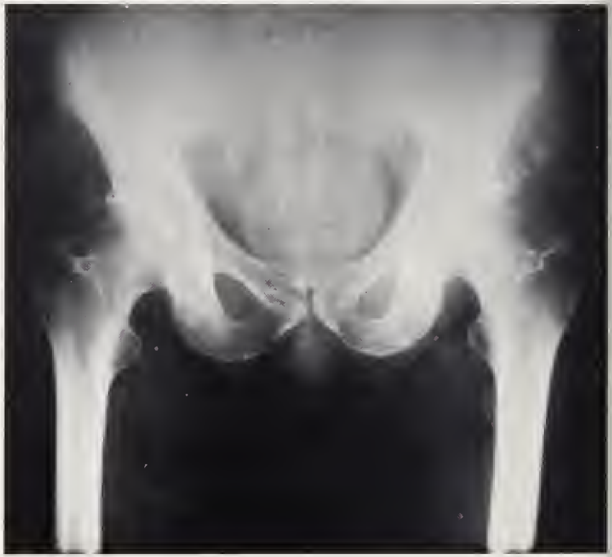

FIG. 4. The postoperative x-ray shows no evidence of further bone destruction.

outer cortex of the ilium and the bone was thoroughly curretted, removing all infected and devitalized tissue. The wound was packed with gauze which was brought out through the lateral edge of the wound. The skin was closed primarily after wide undermining of the abdominal wall. The operative cultures again grew Pseudomonas. Following surgery the patient was treated with six weeks of intravenous Piperacillin®, in doses of 4 gm every four hours. Starting on the second postoperative day, the gauze packing was slowly advanced, being completely removed by the tenth day. The wound drained serosanguinous material for approximately 32 days, at which time it closed spontaneously. He began partial weight-bearing with crutches at 28 days and was discharged home on the 48th postoperative day, fully ambulatory and pain-free. Radiographic studies done prior to his discharge showed no evidence of further bone destruction secondary to osteomyelitis (Fig. 4).

Discussion

The above case illustrates two unusual complications in the donor site of a groin flap: 1) nerve injury, and 2) infection with subsequent osteomyelitis.

This emphasizes the need for a working knowledge of the anatomy of the area as well as careful dissection of the flap in the proper plane (8). Whether this dissection is begun laterally or medially, the flap should be raised at the level of the deep fascia. When the sartorius muscle is reached, the fascia overlying it must be incised and included in the flap, as the vessels lie in this fascia. The lateral cutaneous nerve of the thigh is a branch of the lumbar plexus derived from L 1, 2 and 3. The nerve enters the thigh deep to the fascia lata, after piercing the inguinal ligament near the anterior superior iliac spine. It divides into anterior and posterior branches that pierce the fascia lata separately an inch or two below the lateral end of the inguinal ligament. The anterior branch contains all the L3 component that is in the nerve, and is distributed along the anterolateral surface of the thigh.

There are three principles that make bone infections more difficult to treat than soft tissue infections. 1) There is a small volume of soft tissue surrounded by a rigid wall. An inflammatory response does not have room for expansion and increased pressure causes further bone breakdown and abscess formation. 2) The vascular supply is easily interrupted causing additional necrosis, thus propagating the infection. 3) There is a limited resorptive capacity for necrotic but still mineralized bones, and this makes antibiotic therapy less effective. In children, osteomyelitis occurs most often secondary to hematogenous spread. In the adult, most infection usually results from open wounds associated with either trauma, surgery, or the presence of foreign bodies. This case is unusual not only because the ilium is a rare site of infection, but also because the usual predisposing problems were not involved. Although the graft overlays the ilium, it is unusual for the fascia and periosteum to be involved. In the surgical dissection, osteomyelitis rarely occurs without violation of the cortex itself (9). Dissection in the proper plane and careful attention to details will prevent exposure of the bone injury to the lateral-cutaneous nerve of the thigh.

Summary

Two complications in the doner area of a groin flap are presented. The need for thorough knowledge of the anatomy of the region as well as careful dissection of the flap are stressed.

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Seminars in Reproductive Medicine

Norbert Gleicher, M.D., Editor

Coma Caused by Drug Abuse in Pregnancy

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Abstract

The incidence of drug abuse and overdosage among women of childbearing age is increasing. The immediacy and clinical urgency of the problem is further emphasized when superimposed on the pregnant state. The case reported herein demonstrates the presentation, clinical course, and successful, conservative management of acute glutethimide overdose with coma in the third trimester. A review of the literature follows, dealing specifically with glutethimide overdose. A discussion of the general guidelines for the treatment of drug overdose is offered including current recommendations and specific management features for glutethimide overdose. The conclusion addresses the implications of conservative verses aggressive management for both mother and fetus as an aid to the practicing obstetrician.

Introduction

Treatment of drug abuse and overdosage has become an increasingly routine part of medical practice. Reports from seven large university hospitals showed that between 61% and 75% of nonnarcotic overdose victims were female (1–9). The mean ages in these studies were between 31 and 36 years. One study noted that overdosage was of greater severity in women. Almost twice as many women as men (35 to 18) presented in stage IV coma, and women had a 3.5 times greater death rate (14 to 4) than men (8).

It has become obvious that more and more women in their childbearing years are subject to the morbidity and mortality of intoxicant drug overdose. The reasons are not totally clear. An older study (10) stated that while only one in five cases of psychotic illness of the child-bearing period occurs during pregnancy, neurosis and psychosomatic illness are extremely common during pregnancy itself and this in turn might increase the tendency to sedative (hypnotic) tranquilizer usage and possible overdosage.

The purpose of this paper is to report the first documented case of Doriden (glutethimide) overdose in the third trimester and the successful management of both mother and fetus. A discussion of the pharmacology and toxicology of glutethimide follows together with current management controversies and key points of difference in treatment from other sedative/hypnotic tranquilizer drugs. A general schema for the management of drug overdose and coma is presented as an aid to the clinician.

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Case Report

A 28-year-old Hispanic female Gravida 2 Para 1001, estimated date of confinement within the following two weeks, was found lying on the floor after ingesting from eight to fifteen 500 mg tablets of glutethimide. She was taken to the City Hospital Center at Elmhurst Emergency Room four to five hours after ingesting the drug. On arrival, she was observed to be in stage I coma (by the criteria of Reed, Driggs, and Foote (39), Table I) only minimally responsive to painful stimuli, with spontaneous but sertorous respiration. On admission, vital signs revealed a rectal temperature of 98.0°, pulse 128/min, respiration 16/min and blood pressure 112/80. Upon physical examination, the pupils were minimally dilated and mid positional—only sluggishly reactive to light; corneal reflexes were present bilaterally. The cardiac and pulmonary examinations were within normal limits. Further neurologic examination revealed 2 plus deep tendon reflexes in the upper extremities with 1 plus deep tendon reflexes in the lower limbs; Babinski's sign was not elicited. Abdominal examination showed a fundal height about 2 to 3 finger breadths below the xiphoid, consistent with an intrauterine pregnancy of 36 to 38 weeks. A scar from a previous cesarean section was present. The uterus was nonirritable. The fetal heart was located in the left lower quadrant with a regular rate of 135 beats per minute without any noticable decelerations. On pelvic examination the cervix was found to be soft, long, posterior, and fingertip dilated. The vertex was presenting and was noted to be floating. Previous cesarean section had been for cephalopelvic disproportion and resulted in the birth of a full-term healthy male child. No history of drug or alcohol abuse could be obtained.

Upon admission, a nasogastric tube was inserted and the patient's stomach was lavaged with a solution of emulsified castor oil and normal saline. The aspirate yielded material that appeared consistent with disintegrating tablets. The patient was given oxygen by nasal cannula (8 liters per minute). Preliminary laboratory results showed the patient's complete blood count and chemistries were all within normal limits as were arterial blood gasses. Glutethimide level was drawn on admission and was reported to be 0.9 mg/dl.

The patient exhibited a short period of increased consciousness with some response to verbal stimuli but quickly lapsed back into coma. She was transferred to the intensive care unit where her trachea was intubated. She was permitted to breath spontaneously on a T-piece. Gastric lavage was repeated with clear return. Urine output and fetal heart were monitored. A chest x-ray revealed bilateral pulmonary infiltrates in right upper and left lower lobes. The patient was given methylprednisolone I.V., 1 gram stat and 200 mg every four hours along with penicillin G 600,000 units every 6 hours by I.V. infusion. Sorbitol 60 ml was administered via nasogastric tube to increase intestinal motility. Fluid replacement at the rate of 100 ml/hr with Dextrose 5% in ½ normal saline with 15 mg KCl was started. Furosemide, 20 mg was administered I.V. to increase urine output.

It was planned to continue the pregnancy as long as the patient's condition remained stable. In the event of deterioration, emergency cesarean section would be performed.

Twenty-four hours after admission the uterus was found to be slightly irritable, but pelvic examination was unchanged; the fetal heart rate was 156 per minute with good variability. However, the patient's PaO_2 decreased to 60 torr despite an FiO_2 of 0.5. As the patient's pulmonary status was deteriorating secondary to aspiration pneumonia, it was decided to perform an emergency low flap, transverse cesarean section. Anesthesia was maintained with oxygen, nitrous oxide, and a succinylcholine infusion. The newborn was a 3520 gm female with Apgar scores of 6 and 8. The child was suctioned, stimulated, given oxygen by mask and was rushed to the neonatal intensive care unit, where, because of shallow respirations (vital signs, respiratory rate 80 per minute; heart rate 140 per minute; temperature 97.6° rectally), general lethargy, poor muscle tone, and reactive but sluggish pupils, she received a complete two volume (560 ml) exchange transfusion one hour after birth. The cord glutethimide level pre-exchange was 0.9 mg/dl, and post-exchange was found to be 0.752 mg/dl, and four hours later it was 0.2 mg/dl. During hospitalization, the child also experienced delayed passage of meconium secondary to paralytic ileus and urinary retention but her course was otherwise uncomplicated.

Shortly after delivery, the mother was hyperventilating with a respiratory rate of 32/min and with a blood pressure of 110/80.

Arterial blood gases showed a pH of 7.32, P_aCO_2 of 38 torr, P_aO_2 of 60 torr, bicarbonate level of 20 Mm/l, and S_aO_2 of 87%. A repeat chest x-ray showed right upper and left lower lobe consolidation. Arterial blood gases at this time with the patient breathing spontaneously on a T-piece, with an F_iO_2 of 0.5 showed a pH of 7.4; P_aO_2 was

97 torr, P_aCO_2 27 torr, bicarbonate of 17 Mm/l with an S_aO_2 of 96.5%.

Twenty-four hours after surgery, the patient regained consciousness and was able to respond to questions with gestures. She was stable and responded well to supportive care. Her trachea was extubated and her foley catheter was removed. She was restless with diffuse inspiratory rhonchi; the nasogastric tube was left in place and she was allowed to be out of bed. Arterial blood gases measured with the patient on a ventimask (40% oxygen) were normal. On the sixth day, the patient was transferred back to the obstetrical ward. She was discharged from the hospital on the sixteenth day. The child was discharged four days later. A two-month follow-up of the infant revealed normal growth and no residual effects of the glutethimide intoxication.

Discussion

General Pharmacology and Toxicology

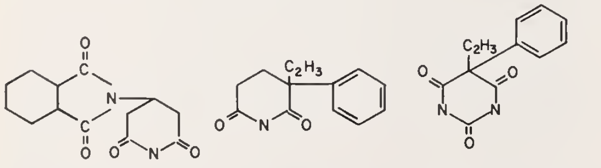
Glutethimide was introduced in 1954 as a sedative/hypnotic which would cause little or no respiratory depression and had a low abuse potential. Structually similar to thalidomide and phenobarbital (Fig. 1), it has metabolic and dispositional pathways different from both (11, 12).

In spite of the structural similarity to thalidomide, rare reports of the birth of malformed children to women who had been taking glutethimide during the critical periods of early pregnancy must be interpreted cautiously, and the possibility of their being coincidental considered (12). There is little likelihood that glutethimide is teratogenic (13).

After ingestion of one 500 mg dose of glutethimide, peak plasma levels are reached in one to six hours. The drug is very slowly absorbed from the GI tract owing to its poor solubility in water. Absorption can be significantly enhanced by ingestion of alcohol (14). However, once absorbed, it very quickly becomes concentrated in the lipoid organs, such as the brain and adipose tissue, with a volume of distribution larger than that of body water. From these stores, the drug gradually recirculates until it is carried to the liver, its main site of detoxification and inactivation. This type of recirculation from lipid stores is reminiscent of the redistribution that takes place after the I.V. administration of the highly lipid soluble, ultrashort acting barbiturates.

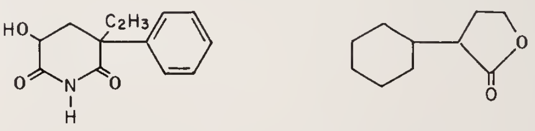
Greater than 90% of ingested glutethimide is conjugated in the liver as two different hydroxylated glucuronides which are in equilibrium with glutethimide in the lipid depots (15). An enterohepatic circulation and systemic recirculation of these metabolites exists and, while generally disclaimed (15), may be responsible for the phenomenon of "glutethimide rebound" (16). Two metabolites recently found to accumulate in the plasma and urine of intoxicated patients are 4 hydroxy-2-ethyl-2-phenylglutarimide (4HG) (17–19) and alpha-phenyl-gamma-butyrolactone (20) (Fig. 2). They do not fulfill the characteristics formally established for glutethimide's metabolic products and are not less readily absorbed nor more quickly excreted by the kidneys as formerly believed (21).

In addition, 4-HG has been found to have twice the parent compound's pharmacologic activity in producing drug-induced ataxia in mice. A case report of a patient in coma for 48 hours observed that while serum levels of glutethimide fell, the patient remained in coma long after subtoxic levels were present and this correlated with the time when levels of 4-HG were elevated in blood samples (22). Clinical recovery more closely approximated the time when 4-HG levels were falling. Thus, a contributory effect of 4-HG either alone or synergistically with the parent compound in prolonging coma must be considered. Alpha-phenyl-gamma-butyrolactone, found to be nonpolar and highly lipid soluble, appears to cross the blood-brain barrier quite rapidly. Its elimination from body tissues is also decreased because of these attributes and thus its presence contributes to the half-life activity of the parent compound. Moderate levels of this metabolite were found to cause significant respiratory problems in test animals. Thus, enterohepatic circulation of these metabolites, in addition to the unpredictable re-



THALIDOMIDE GLUTETHIMIDE PHENOBARBITOL

Fig. 1.



4-HG ALPHA-PHENYL-GAMMA-BUTYROLACTONE

Fig. 2. Metabolites.

lease of glutethimide from lipid stores (because of its high oil/water partition coefficient) may contribute to the fluctuating clinical course often seen in intoxicated patients. While plasma levels of glutethimide may fall, increasing levels of active metabolites which are capable of entering the central nervous system may add their effects so that a patient apparently recovering, responsive and breathing unassisted, may suddenly become apneic and lapse back into coma. Other explanations for "rebound" have been postulated (16), such as recovery of depression of gastrointestinal motility and further absorption of the drug, but transport of drugs across the intestine proceeds even when the gut tissue is denervated or excised and thus makes this untenable.

Concentrations of glutethimide in the urine are always lower than those in plasma and less than 2% of the drug is excreted unchanged in 24 hours by this route (23).

Concentration of drug in breast milk is very low, but glutethimide crosses the placenta readily so that maternal and fetal plasma concentrations are similar (23). The spontaneous decline in blood levels follows a biphasic curve with an initial rapid, and a later slow phase. The mean half-lives during these periods are 3.8 and 11.6 hours respectively (23, 25). This is in contrast to a prolonged mean serum half-life of 40.1 hours found in a series of patients with glutethimide overdose (24). Although up to 54% of the drug has been claimed to be bound to plasma proteins in vitro (23), the oil/blood partition co-efficient of 5 indicates that plasma proteins probably do not inertly bind significant amounts of glutethimide (25). Finally, it is known that glutethimide has marked anticholinergic activity and is capable of inducing liver enzymes.

Toxicology

Glutethimide was accepted in the late 1950's because of its claimed advantages over the barbiturates in terms of lesser addiction potential and withdrawal symptoms. By 1956, glutethimide was the sixth most frequently prescribed sedative (26). In fact, glutethimide has been used as an analgesic and sedative in obstetrical practice for approximately ten years prior to 1969 (27, 28, 90). By the mid-1960's, it was clear that glutethimide would not replace the barbiturates as an all purpose sedative/hypnotic since it could lead to significant dependence, was frequently abused, and was potentially toxic if used chronically (29). It appears to be prescribed today in sufficient quantity for it to appear in many studies as the second most common nonnarcotic agent after the barbiturates producing drug overdosage with or without coma, requiring hospitalization (1, 4, 8). The mortality from glutethimide ingestion is consistently greater than that for any other drug in the sedative-hypnotic-tranquilizer group (8, 26, 30, 31). In some of the studies cited, a large percentage of patients with glutethimide overdose presenting in stage 4 coma died as compared to those with similar presentation from overdose with other agents. Ingestion of dosages exceeding 5 to 10 grams may lead to serious or fatal complications and ingestion of greater than 10 grams is associated with significant mortality (34).

Several investigators have outlined the variability in the clinical picture following glutethimide intoxication (32, 33). The spectrum may include one or more of the following: profound coma distinguished from other drug-induced comas by the occasional appearance of lateralized or focal neurologic deficits accompanied by cyclic variations in coma depth; simple mydriasis with light reactivity to fixed dilated pupils (unilateral or bilateral); papilledema; periods of sudden apnea (often seen during gastric lavage); hypotension (which may lead to shock and hypothermia); hyperthermia; convulsions; areflexia; and pulmonary and cerebral edema (sometimes also seen with overzealous treatment). Other less severe but problematical symptoms include: xerostoma, emesis, paralytic ileus, urinary bladder atony and occasional muscular spasms and twitching. Several investigators have reported that patients with intubated tracheas or those with tracheostomies have had thick tenacious bronchial secretions which require constant suctioning. This occurred in spite of the strong anticholinergic effect of the drug and has contributed to the deaths of several patients (8).

Complications may appear quite unexpectedly with periods of apnea occurring in the face of apparently lessening depression of the central nervous system.

Maher (24), noting the remarkably prolonged coma seen in intoxicated patients, found a positive correlation of serum half-life with serum level suggesting that coma would be unduly prolonged at high serum levels. A possible explanation is that, at high serum levels, metabolism of glutethimide may be delayed by rate-limited enzymatic degradation. He also reported that the serum half-life was often longer in the intoxicated, hypotensive patient than in the normotensive patient. Impaired perfusion of tissues, especially the liver, which normally degrades glutethimide, may account for prolonged elevation of the serum level in some instances. Others have reported little apparent correlation between blood levels of the drug and the clinical condition but this may be due in part to the wide range of tolerance among individuals because of differences in metabolic proficiency with continued use or abuse (3, 36). Other investigators have reported comparative serum and cerebrospinal fluid concentrations of glutethimide in an attempt to explain the relationship between them and the unique, fluctuating clinical course observed in comatose patients (37, 38). Although cerebrospinal fluid levels were not observed to exceed 0.8 mg per deciliter in the small number of patients studied, blood levels and pattern of change in neurologic status varied considerably (37). The authors concluded that perhaps the best estimate of the duration of coma, seems to be the maximum glutethimide concentration found upon admission. In fact, there did seem to be a definite relationship between the rate of decrease in serum glutethimide with the maximum concentration attained in serum. This still does not elucidate the contribution of metabolites to the clinical course.

Prognosis

There have been several reports attempting to correlate presenting symptoms with prognosis in cases of severe poisoning. One of the problems of interpreting such data has been the different criteria used to classify the degree of CNS depression and coma when it exists. Two classifications (both originally established for coma from barbiturate intoxication and now applied to other drug-induced comas as well) are illustrated below for comparison (Table I) (39, 40).

In addition to obvious problems of classification and characterization, many studies and case reports failed to determine accurately the dose ingested, the time elapsed to admission, and even blood levels before and after treatment. Studies from which mortality rates have been frequently quoted deal with the most seriously intoxicated patients and these statistics should not be used to characterize other patients admitted in less critical condition (41) as therapy should be tailored to the clinical situation.

A report dealing with accumulative prognostic indices for patients with drug overdose admitted in coma utilized hemodynamic, metabolic, and respiratory measurements and subjected this data to univariate and multivariate analyses (6). It was found that monitoring systolic pressure and mean central venous pressure along with pH were the best variables to initially predict survival. Later, arterial oxygen saturation and blood lactate levels were helpful in predicting final recovery. In all cases, the systolic pressure was the single most useful measurement for predicting survival. While the construction of mathematical formulae to determine the probability of survival for indices such as these may bear fruit in the future, it seems that the physician's clinical judgement supplemented by some quantitative physiologic measurements should remain the cornerstone in assessing severity and evaluating the patient's response to treatment.

A retrospective study at the Massachusetts General Hospital also attempted to establish cor-

TABLE I

Classifications of Drug induced Coma

Criteria of Reed, Driggs & Foote (39)		Criteria of Matthew & Lawson (40)	
Stage 1:	Patient comatose but responds by withdrawal to painful stimuli (pinching, venipuncture). DTR's intact. No depression of respiration or blood pressure.	Grade 1:	Drowsy but responsive to verbal stimulation.
Stage 2:	Patient does not withdraw from painful stimuli. Most or all DTR's intact. No depression of respiration or blood pressure.	Grade 2:	Patient responds only to mild painful stimuli.
Stage 3:	Most reflexes depressed or absent. Respiration and blood pressure not depressed.	Grade 3:	Minimum response to maximum painful stimulation.
Stage 4:	Most reflexes depressed or absent. No response to verbal or painful stimuli. Patient has respiratory depression with cyanosis or circulatory failure and shock or both.*	Grade 4:	No response to maximum painful stimulation.

* Stage 4 above has been further modified by Arieff and Friedman (8) to include: Respirations depressed to less than 8 per minute and/or the systolic blood pressure falls to less than 85 torr.

relates of outcome following acute glutethimide overdosage (1). Variables were selected for mathematical analysis but included not only factors directly related to clinical outcome but also factors such as sex, age, dose ingested, and ingestion of other agents. The findings confirmed that serious and fatal poisoning commonly results from ingestion of glutethimide. A concentration of 30 micrograms per ml was always associated with a coma grade greater than 2 (40) and a dose of 10 grams or greater was associated with a coma grade of 3 or 4 in 11 of 13 cases. Sixty-two percent of patients were female; six died. Age was the most important determinant of survival. Glutethimide dose was also the major determinant of the need for endotracheal intubation. The authors stated that the plasma glutethimide concentration or the estimated ingested dose, or both, do have some value as predictors of serious central nervous system depression while the converse is not always true. It was noted, however, that a relatively small ingested dose or a low plasma level by no means ruled out the development of serious intoxication, particularly in those patients who also ingested barbiturates. Another report in which neurologic data were reduced to ten measurements of brainstem function sought to establish neurologic and electroencephalographic correlates in glutethimide intoxication (42). The patient was in grade 4 coma and received complete neurologic assessment every other hour over 45 hours. Spinal reflexes, pathologic reflexes, muscle tone, and response to nociceptive stimuli were omitted from the 10 measurements used to derive the brainstem index. Interestingly, respiratory depression, present for at least eight hours after admission, showed some tendency to recur in association with lowest values of the brainstem function index. Since $PaCO_2$ values never exceeded 45 torr and the PaO_2 never dropped below 60 torr at these points, the authors suggested that the variations in serum glutethimide concentration caused the fluctuations in brainstem function and caused the respiratory changes observed. Recovery of brainstem function proceeded in a generally caudal to rostral direction but return of pupillary light reflexes was preceded only by the resumption of spontaneous respiration.

Treatment

The steps outlined below are for the treatment of most types of drug-induced coma (44–46). Because of factors unique to glutethimide and some of the controversies that exist surrounding treatment in the overdose situation, the first step in management should be directed toward instituting intensive supportive care of the patient with attention to the most commonly encountered complications. A cuffed endotracheal tube should be inserted. In addition, mechanical ventilation with humidified room air or enriched oxygen should be available and the patient should be placed in a setting where he can receive quick and capable support when needed. Meticulous and constant endotracheal toilet is strongly emphasized. Analeptics have absolutely no place in the treatment of glutethimide-induced respiratory depression. It should be considered that the complications of analeptic agents include seizures, cardiac arrhythmias, hyperpyrexia, and hypoxic brain injury (8). Circulatory status should be evaluated as expeditiously as possible. While blood is being drawn for toxicology, fluid therapy with normal saline or lactated ringer's solution should be started through one and preferably two large-bore peripherally placed catheters. If there are signs of hypotension and/or shock, fluid therapy must proceed cautiously since glutethimide is believed to be a vasomotor depressant causing relative hypovelemia secondary to peripheral vaso-dilatation as do the barbiturates. Response to fluid therapy for hypotension has resulted in pulmonary edema in a significant number of patients whose central venous and arterial blood pressures remained low (8). Attempts to correct hypotension by infusion of vasopressors such as norepinephrine (4–8 mg in 500 ml of D5W by constant intravenous drip or metaraminol, 100 mg) have been successful.

A constant record of arterial pH, pO_2, pCO_2, blood pressure, and hourly urine output should be kept. As soon as a large volume of urine is available it should be sent for toxicology. The central venous pressure should be monitored. Electrocardiographic monitoring is mandatory. While supportive care alone has been associated with the lowest incidence of morbidity and mortality, complications appear to increase in proportion to the duration of coma (43, 44). Therefore, the duration of coma should be diminished whenever possible. When the patient is stable and is receiving adequate respiratory, cardiac, and circulatory support and fluid and electrolyte imbalances have been corrected, measures to facilitate removal of the agent should be instituted. Alkaline gastric lavage is indicated in glutethimide overdose because its high pKa of 9.0 would tend to impair passage across the gastrointestinal wall. Hydrolysis and consequent water solubility of glutethimide are potentiated in alkaline solutions and the strong anticholinergic effect of the drug increases its residence time within the lumen of the gastrointestinal tract (34). A nasogastric tube should be placed for this purpose. The presence of the cuffed endotracheal tube protecting the trachea and lungs (13) is also recommended. Gastric and duodenal aspirates should also be sent for toxicologic identification and quantification. As previously stated, caution is advised since many patients have experienced sudden apnea during the manipulations that lavage entails. Lavage with castor oil may be more effective than appreciated. Due to its poor water solubility and high lipid solubility, undissolved residue may be taken up preferentially by the lipid perfusate and be more readily removed. In contrast to the barbiturates, whose absorption is usually rapid (gastric aspiration and lavage are probably ineffective three to four hours postingestion), lavage is certainly worth one or two attempts in the case of glutethimide even if ingestion is presumed to have been greater than four hours previously. Others have also recommended castor oil catharsis theoretically propelling the dissolved drug more rapidly through the GI tract diminishing time for absorption, but this has not met with wide acceptance (47).

Activated charcoal has been used to prevent the gastrointestinal absorption of glutethimide (48). It has been reported that 1 gram of activated charcoal is capable of absorbing 50 to 60 mg of glutethimide (49). Administration of large amounts of charcoal in an aqueous slurry via nasogastric tube may be effective if performed within hours after ingestion. Unfortunately, forced alkaline diuresis has been of little help in removing significant amounts of glutethimide rapidly enough to shorten the duration of coma. Curry (23) has reported the normal glomerular filtration rate for glutethimide after therapeutic dosage and after correction for mean protein-binding and for a mean glomerular filtration rate of 12.5 ml per minute was 78 mg/min. While higher rates of clearance and significant amounts of drug have been removed only after many days of treatment (50), this modality is best reserved for those drugs that achieve higher blood concentrations and whose pKa's are attainable by alkaline manipulation of blood pH (example: long acting barbiturates). It should be noted that while IV mannitol (25 to 50 grams) has been reported to be possibly effective in correcting the cerebral edema known to develop in some patients, the administration of large quantities of intravenous fluids to maintain a high urinary output may be counterproductive and cause pulmonary edema even when the CVP is low. The same principle should be remembered in treating the hypotension so frequently encountered in patients overdosed with glutethimide. Of course, renal and cardiac failure preclude the use of forced diuresis. While many animal and human studies on biliary diversion have reported no effect on absorption, excretion, or clinical manifestations of the active form of the drug, recent studies on the metabolites of glutethimide (17–19) and their possible synergy with the parent compound in producing and prolonging coma may rekindle interest in attacking the enterohepatic circulation as a therapeutic modality.

Perhaps the most hotly debated issue in the literature concerning management of glutethimide overdose concerns the use of dialysis (59). While most reports have deprecated the effectiveness of peritoneal dialysis as blood levels are usually low four to six hours postingestion, several case reports have demonstrated efficacy and perhaps the technique should not wholly be abandoned, especially in situations when hemodialysis is not available and time is required to transfer the patient to better equipped facilities (51–56). Peritoneal dialysis seems to be most efficient when the concentration gradient between blood and peritoneal fluid is high, earily in the intoxication (57).

It has been suggested that hemodialysis should be considered in any patient who has ingested over 10 grams of glutethimide or who has a blood level of over 3 mg/dl (58). While aqueous hemodialysis is effective in removing glutethimide and clearances ranging from 24 to 149 ml per minute have been reported (60), clinical response as compared to that seen in barbiturate overdose has been less dramatic (31). However, Maher has reported in intoxicated patients in whom serum half-life averaged 40.1 hours, treatment with hemodialysis was effective in shortening the half-life to 14.6 hours (24). The important factor again seems to be early dialysis since later dialysis may be limited by large distributional space especially in fat depots which seem to increase with time. Some authors have claimed that protein binding may limit the removal of glutethimide but this does not seem likely. While large amounts of the drug and its metabolites may be present in lipid organs and in the central nervous system, the commencement of hemodialysis and removal of the glutethimide present in blood will cause a redistribution and re-equilibration to take place and should theoretically aid in more rapid disposal of the drug. In addition, hemodialysis may provide a circulatory stimulant action aiding perfusion of key metabolic core organs such as the liver and kidneys.

Studies on the use of aqueous hemodialysis have documented a shortened length of coma and serum half-life as well as increased dialysate recovery over peritoneal dialysis and removal rates 30 to 200 times that of urinary excretion of the drug (21, 31, 61–63). In severe poisoning, an extended dialysis or the use of dialysis in series may be required (64). Mortality rates in severe cases have been reported to be reduced from 50 to 18 percent with hemodialysis (31, 65, 66). Despite these studies indicating the efficacy of hemodialysis other authors, notably Chazan and Cohen (3), have published conflicting reports regarding the correlation between glutethimide levels and the level of coma or the complexity of the clinical course. In their initial report of 37 patients, 17 were severely intoxicated, five were treated with prolonged hemodialysis and were contrasted with the other 12 who were treated supportively without hemodialysis (3). From this comparison, the authors found no evidence that hemodialysis shortened the duration of coma, lessened complications, or improved survival. In a subsequent prospective report, the same authors reported 70 cases of glutethimide poisoning treated without hemodialysis—more than half of whom were responsive upon admission and had no significant morbidity or mortality (4). Although they reported CSF levels were linearly correlated with blood glutethimide levels (being approximately 60% of the blood values), the authors failed to observe any apparent relationship between duration of coma and glutethimide levels on admission or between state of consciousness and subsequent changes in blood levels. Nevertheless, those patients who were comatose on admission sustained considerable morbidity, including hypotension in 42%, respiratory failure in 32%, and pneumonia in 35%. The authors concluded that hemodialysis may be of value in some patients with glutethimide overdose.

In another study of 31 consecutively managed patients, in which 13 presented in grade 3 or 4 coma, the overall mortality was found to be 3%. It was concluded that hemodialysis is not essential in the management of severely poisoned patients (2).

Several comments, however, should be made concerning the lack of correlation between blood glutethimide levels and state of consciousness reported by these authors. First, the amount of glutethimide present in blood and effectively removed by hemodialysis diminishes with time as it takes up residence in adipose tissue and the central nervous system; therefore, the expeditious institution of dialysis is more likely to result in a more clinically appreciable change in state. Secondly, the authors make no mention of the contribution of metabolites to the clinical picture and the fact that glutethimide levels may fall for a time while metabolite levels are rising and coma continues to fluctuate until both levels fall off. Thirdly, a patient ingesting glutethimide over a long period might adapt to the drug with enzyme induction and thus be expected to have fewer toxic symptoms at the same blood levels than patients not tolerant to the drug. Finally, responses of the central nervous system and circulatory system to a given dose of glutethimide apparently also depend upon individual factors such as age and pre-existing diseases of the liver or heart as well as habituation (5).

Since morbidity in over-dose patients tends to correlate with the duration of coma and hemodialysis is known to decrease this period in glutethimide poisoning, conservative therapy should be reserved for those patients presenting clinically in lesser stages of coma and in those responsive to initial supportive measures. A Danish study (5) corroborated the general view that the incidence of pulmonary complications increases with the duration of coma, as deaths occurring after more than 36 hours of coma were caused by pneumonia and atelectasis. The ascent in mortality rate with age reported was considered to be caused by an increasing incidence of pre-existing heart disease, with hypotension representing the major risk factor (5). In a review of nearly 600 patients suffering from acute drug overdose, it was found that 59% of the fatal cases died not from the toxic substance itself, but from pulmonary complications (25, 67). Thus, it behooves the clinician to resuscitate the patient as soon as possible. Clinical guidelines that may be used to decide when to use dialysis in patients with glutethimide overdose are listed in Table II.

Lipid hemodialysis holds promise and higher removal rates of drug both in vitro and in vivo have been reported (69, 70). Another researcher has studied the effect of lipid and aqueous dialysis as well as peritoneal dialysis with albumin in a patient with severe glutethimide poisoning (71). He found lipid dialysis (glutethimide clearance 40 ml per minute) was three times more effective than peritoneal dialysis and that 24-hour peritoneal dialysis with 5% albumin was comparable to six hours of aqueous hemodialysis.

Hemodialysis with activated charcoal, while formerly found to be more adsorbent for the barbiturates than glutethimide, has been found to significantly enhance glutethimide removal in

TABLE II

Indications for Hemodialysis in Glutethimide Poisoning (25, 68)

1. A blood level of more than 3 mg/dl
2. Ingestion of more than 10 grams or 0.15 gm/kg body weight
3. A patient in profound coma (grade 3 or 4) or manifesting cerebral or pulmonary edema or fixed dilated pupils or areflexia
4. A patient with multiple drug ingestion
5. Refractory hypotension
6. Evidence of hepatic damage and/or renal insufficiency
7. Progressive clinical deterioration in spite of all other treatment
8. Patients with lesser grades of coma who show no improvement

vitro when added to the dialysate (72). Hemoperfusion using uncharged macroreticular copolymers with specific adsorptive attraction for lipid soluble, organic molecules has been claimed to be highly effective in clearing blood of glutethimide, as well as phenobarbitol and other barbiturates, ethchlorvynol, and methaqualone (73). A recent study detailing the use of hemoperfusion through fixed-bed activated charcoal cartridges for 54 severely overdosed patients (including 11 glutethimide poisonings) found its greatest efficacy in the treatment of phenobarbitol toxicity (7). Of the 11 patients with glutethimide overdose, nine had aspiration pneumonia, four required vasopressors to support their blood pressures; all needed endotracheal intubation, and five required tracheostomy for maintenance of ventilation. The periods of therapy with hemoperfusion ranged between two and one half and six hours and six patients required a second hemoperfusion. While the treatment procedure did not result in as rapid or apparent a change in the degree of coma as seen in those with phenobarbitol overdose, substantial amounts of the drug were removed during these therapeutic courses. This is probably due to the continuous release into the blood of drug sequestered in adipose tissue. This is supported by the observation that the levels of these agents in the blood either did not fall or fell only moderately despite removal of substantial amounts of glutethimide or short-acting barbiturate (7). The major drawbacks of hemoperfusion have been systemic platelet destruction—in some cases up to 40% of the circulating supply—and a lowering of serum calcium and phosphorous levels (7). The indications for hemoperfusion are the same as those for dialysis but with continued refinement this technique may one day replace hemodialysis as the therapeutic modality of choice in acute life-threatening drug overdose.

Discussion

In 1974 and 1975, there were 4,694 accidental deaths caused by poisoning in the United States and approximately 4,500 accidental and intentional deaths occurred in the United Kingdom in 1973, (25, 74–76), in most cases before the patient reached the treatment facility. On the other hand, acute self-poisoning accounts for ten to 11.3 percent of all medical emergencies presenting in hospitals in the United Kingdom, with a distinct female preponderance (77, 78). In the United States in 1975, there were 26,148 deaths caused by the intake of medicinal and nonmedicinal substances of which 14,925 were caused by analgesic and antipyretic agents (79). In the same year in the United States, an estimated 314,000 patients were discharged from nonfederal short-stay hospitals with a first listed diagnosis of poisoning by medicinal and nonmedicinal agents (80). Deaths reported for accidental poisoning with drugs and medicinals in the U.S. in 1977 numbered 2,214, while suicides caused by poisoning accounted for 6,487 (35). Comparative inpatient statistics for the United Kingdom show that in 1973, nearly 119,000 patients were discharged with a diagnosis of poisoning (81, 82). These figures do not take into account minor poisoning, disclosed by the Health Interview Survey, National Center for Health Statistics, which estimated an incidence of 6.2 million poisonings by medicinal and nonmedicinal agents in 1975. In the United States motivation for self-destruction from drug abuse shows a strong female tendency, while dependence on and motivation for psychic effects of drugs exhibits a male tendency (83, 84). Moreover, about two million poisonings and 400 deaths occur in children yearly in the United States (85). The overall mortality rate from poisonings in hospitalized cases is low, usually less than 1% of those admitted (86). This low mortality has been ascribed to the adoption of intensive supportive care. However, the contribution to mortality in large series is mainly derived from those patients in stage 4 coma principally because of narcotic and sedative poisoning (87, 88). Stage 4 coma still has appreciable mortality variously reported to range from 5% to 34% in several series despite intensive supportive care (8, 87). It is in this group that dialysis or hemoperfusion may play a significant role as an adjunct to expert supportive therapy (25).

Frequently, as in this case, patients incurring drug overdose or poisoning are critically ill and may require multidisciplined therapy. A coordinated team of physicians including obstetrician, anesthesiologist, pediatrician, intensive care nurses, a psychiatrist and social worker were all involved in administering primary and follow-up care to insure the recovery and well-being of both mother and child and to effect the complete rehabilitation of the patient.

The case herein illustrates many points key to the management of drug overdose. Of major importance is the realization that the treatment of drug overdose in pregnancy does not differ significantly from that in the nonpregnant state. The hazards and difficulties of glutethimide overdose and its treatment have been recorded as unusually complex and were especially so in this patient in the third trimester of pregnancy. Of major concern, after establishment of an airway, central and peripheral intravenous lines, and methods to retrieve unabsorbed drug, was the patient's pulmonary and circulatory status. That she was breathing spontaneously on admission and was in a light stage of coma was of little consolation. While her vital signs and the fetal heart were stable, there was sufficient rationale to treat conservatively and expectantly. When, however, the mother's respiratory status worsened, most probably secondary to the combined effects of drug intoxification and aspiration pneumonia, expeditious emergency delivery of the child was believed to be mandatory. Any hypotensive or apneic episode could have had serious consequences on the fetus whose normal blood gases and blood pressure are quite low to begin with (normal values when the mother is breathing room air determined by sampling of the umbilical vein usually show a PaO_2 ranging between 23 and 32 torr, $PaCO_2$ between 40 and 50 torr, pH 7.3 to 7.35, and a blood pressure of 28 torr; pressure in the venous sinuses is only 5 torr while that of the intervillous space is 10 torr) (90). Any maternal respiratory or perfusion embarrassment could upset the delicate balance between maternal and fetal oxygen and nutrient exchange. Irregular uterine contractions, if of sufficient force, could appreciably diminish perfusion of the intervillous space. An intrauterine contraction of 30 torr is sufficient to reduce the intervillous circulation by 50% and a contraction greater than 40 torr is sufficient to completely stop perfusion and therefore subject the fetus to hypoxia (90). The normal blood flow to the intervillous space at term is between 350 and 550 ml per minute, however, the capacity of the intervillous space at term is only 150 ml and the amount of O_2 in this reservior is sufficient for only about one to two minutes (90). The flow of blood within this space is also slow—between 0.1 and 10 ml/sec—which tends to delay transfer of drugs via the placenta from mother to child; however, it also tends to bring the fetal and maternal blood levels into equilibrium if drug is present for or administered over a prolonged period of time. This is amply demonstrated in the present case in which maternal and newborn blood levels of glutethimide were identical. Thus, when the patient developed respiratory insufficiency and also began to have irregular uterine contractions, rather than subject the fetus to hypoxia, it was believed that immediate delivery was indicated. While the child's delivery was uneventful, and she received Apgar scores of 6 and 8, later in the neonatal ICU, the child was observed to be in respiratory distress and quite depressed. This is somewhat reminiscent of the phenomenon seen in neonates born to mothers who are habituated to barbiturates and who deliver normal healthy children with good Apgar scores who later develop withdrawal symptoms (91). In the present case, however, the child was hypoexcitable with depressed reflexes, respiration, and decreased nutritive sucking, and later developed the expected anticholinergic side effects of glutethimide including ileus manifested by delayed passage of meconium and urinary retention. Presumably, as the infant is separated from the maternal source of efficient liver detoxifying enzymes and circulatory support, it is left to metabolize the glutethimide sequestered in its tissues with its own immature microsomal enzyme system and sluggish circulatory, renal, and ventilitory effort. Glutethimide is known to induce the activity of the microsomal enzyme, uridine diphosphoglucuronyl transferase, but not when administered acutely. The authors were able to find only one other case of neonatal respiratory depression reported in the literature to be caused by glutethimide (27). As mentioned previously, glutethimide was used extensively in obstetrical practice and considered safe, causing negligible effects on the newborn or mother when used in therapeutic dosage (28, 92). In the case referred to above, one gram of glutethimide was administered orally about four hours before delivery with 50 mg of meperidine given intramuscularly 45 minutes prior to delivery. The one minute Apgar score was nine but two hours postdelivery the respiratory rate was found to be between 12 and 16 and ventilatory efforts were quite shallow. This neonate also underwent a double volume exchange transfusion and the analyzed sample was found to have a glutethimide level of 0.34mg/dl; however, pre- and postexchange blood levels were not measured in either the child or the mother's blood. Near the completion of the exchange, the child became responsive and later fully recovered. In our patient, initial respiratory rate on admission to the neonatal ICU was 80/min; umbilical vein glutethimide concentration was 0.9 mg/dl. At one hour postdelivery, a complete double volume exchange transfusion was performed using fresh type-specific citrated whole blood. Four hours postexchange, neonatal glutethimide levels had declined to 0.2 mg/dl. While the initial exchange lowered the neonatal drug level relatively little (to only 0.7 mg/dl), in some poorly understood fashion it seems to have stimulated the child's metabolism to more effectively clear the drug and this effect seems independent of renal pathways since urinary retention persisted as respiration and reflex activity improved. Perhaps the exchange transfusion helped bolster perfusion of the liver.

While the role of hemodialysis in glutethimide overdose remains controversial, this case was managed successfully without it. In a strikingly similar case reported, a 21-year-old female estimated to be in her 23rd to 24th week of pregnancy was admitted in stage 1 coma after glutethimide overdose (51). The patient was managed conservatively until three hours after admission when her coma deepened to stage 4 and a ten hour course of hemodialysis was administered. While periods of hypotension and tachcardia occurred both during and following dialysis, the patient's clinical status improved: reflexes returned, respiration improved, and the patient became more responsive. The glutethimide level on admission was reported to be 2 mg/dl and that immediately following dialysis was 0.9 mg/dl. Twenty-four hours after admission and 21 hours after dialysis was begun, the patient was conscious and conversing. She was discharged on the 26th hospital day to return four months later in active labor and deliver a normal male infant weighing 2860 gm. In the present case, the authors can only speculate that had our patient's condition worsened, serious consideration would have been given to initiating hemodialysis in addition to emergency removal of the fetus. Since repeated courses of hemodialysis have been administered in azotemic pregnant females with chronic renal disease during the last trimester with subsequent delivery of viable infants, we see no reason to withhold a procedure which may well be lifesaving for both mother and neonate.

This article has highlighted some of the basic management principles of drug overdose. With the increasing numbers of poisonings reported each year, especially those affecting women of childbearing age, cases such as this may unfortunately become more common. It is equally important for obstetricians as well as pediatricians and other clinicians to be familiar with the therapeutic modalities available to institute the appropriate therapy with minimum delay. While the authors have concentrated specifically on the recognition and management of glutethimide overdose those interested in the treatment of other drug intoxications are directed to the excellent review by Winchester et al (25).

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Ophthalmologic Notes

Keith M. Zinn, M.D., Editor

Vitreoretinal Surgery in a Patient with Sickle Cell Retinopathy

Keith M. Zinn, M.D.

Sickle cell anemia was first described in 1910 (1), but the retinal findings were not reported until 1930 (2). Proliferative sickle retinopathy leading to vitreous hemorrhage was observed in the 1950's (3, 4). Patients with hemoglobin SC, -SS, and -S-Thalassemia are at risk in developing nonproliferative (Table I) and proliferative (Table II) sickle retinopathy. The stages of proliferative sickle retinopathy can begin with mild peripheral retinal arteriolar occlusion and progress to retinal neovascularization (sea fan formation) that may lead to severe vitreous hemorrhage and vitreal membrane formation and end in a severe tractional and/or rhegmatogenous retinal detachment. The staging of proliferative sickle retinopathy is outlined in Table II (5).

Hemoglobin SC was first described in 1950 (6) and recently it has been estimated that there are 36,000 individuals in the United States with this abnormal hemoglobin (6) gene complex (7). Although there are more individuals with hemoglobin SS in the U.S. population, it appears that hemoglobin SC is the most common cause of proliferative sickle retinopathy (5).

Proliferative sickle retinopathy patients who have a retinal detachment require extra surgical care in scleral buckling operations to avoid anterior segment ischemia and localized scleral necrosis (8–12). Interruption of the anterior ciliary artery blood flow in sickle patients has been the postulated mechanism for anterior segment ischemia following scleral buckling surgery (13–15). Avoiding these complications has been accomplished by minimizing scleral buckling and surgical trauma as well as by utilizing preoperative and intraoperative blood transfusions (16) (packed cells) with hyperoxygenation under general anesthesia. In some cases, the hyperbaric chamber has been used to hyperoxygenate the patient during retinal detachment surgery (17–19). Proliferative sickle retinopathy patients have undergone pars plana vitrectomy surgery without untoward difficulty (16, 20) in terms of anterior segment ischemia.

Proliferative sickle retinopathy patients with rhegmatogenous retinal detachments accompanied by dense vitreoretinal membranes will require scleral buckling surgery as well as pars plana vitrectomy. These cases represent complex management problems. One such case of hemoglobin SC proliferative retinopathy is presented to illustrate surgical staging of the scleral buckling and pars plana vitrectomy procedures as one way of avoiding anterior segment ischemia and phthisis bulbi in these highly susceptible patients.

Case Report

Y.T. is a 31-year-old black female who is a registered nurse with a documented history of hemoglobin SC–sickle cell anemia. She was hospitalized in 1977 for a sickle cell crisis and was on folic acid therapy when she presented with sudden loss of vision in her left eye in October 1979. Prior to the visual loss in her left eye, she states that her vision had been excellent in both eyes and there were no antecedent visual symptoms in either eye.

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TABLE I

Ophthalmoscopic Findings of Nonproliferative Sickle Retinopathy
Retinal hemorrhages (salmon patches)
Retinoschisis cavities + glistening yellow spots
Retinal pigment epithelium hyperplasia (sunbursts)
Retinal pigment epithelium atrophy (sunbursts)
Venous tortuosity (marked)

TABLE II

Stages of Proliferative Sickle Retinopathy

	Stage	Vitreoretinal Findings
	I	Peripheral retinal arteriolar occlusion
PROGRESSION	II	Peripheral retinal arteriovenular shunts
	III	Peripheral retinal neovascularization (sea fan formation)
		Vascular leakage of protein + RBC's into vitreous
		Abnormal vitreoretinal adhesion to sea fan
		Vitreous contraction
		Tear of sea fan
	IV	Vitreous hemorrhage
		Secondary vitreoretinal traction
	V	Tractional retinal detachment
		Rhegmatogenous retinal detachment
		Massive periretinal proliferation

Our ocular examination at the time of sudden visual loss in the left eye was as follows:

Visual acuity, without correction, was 20/20 in the right eye and hand motion at one foot in the left eye. Manifest refraction could not improve the visual acuity in either eye. Extraocular motility studies revealed each globe to have full rotations in all standard fields of gaze and the eyes were straight in the primary position of gaze.

The lids ocular adnexae and lacrimal gland apparatus, conjunctivae, corneae, and sclerae were within normal limits bilaterally. The intraocular pressures were 13 mm Hg in the right eye and 10 mm Hg in the left eye by applanation tonometry. Slit lamp examination of the anterior chambers revealed them to be clear and of moderate depth with grade III-IV open anterior chamber angles for 360° and 2+ pigmentation of the trabecular meshwork bilaterally. The irides were brown O.U. and the pupils were equal, round, and reactive to light and accommodative targets.

Both lenses and the right vitreous cavity were clear. The left vitreous cavity had a moderately dense vitreous hemorrhage with some intravitreal membranes. Funduscopic examination on the right revealed a well demarcated optic nervehead with a cup/disc ratio, in the horizontal meridian of 0.2. A crisp foveal reflex with normal macular pigmentation was observed. Approximately one to two disc diameters nasal to the optic nervehead, at about the three o'clock meridian, a discoid-shaped zone of hyperpigmentation was noted at the level of the retinal pigment epithelium. The lesion was flat with sharply defined borders and represented a sunburst lesion characteristic of nonproliferative sickle retinopathy. In the superotemporal quadrant, a zone of retinal neovascularization (sea fan) was present at the equator O.D. There was some venous tortuosity of the retinal vessels in the right eye. Peripheral indirect ophthalmoscopy in the right eye with gentle scleral depression failed to reveal any retinal tears or holes and a zone of 1+ white with pressure was present from the equator extending to the ora serrata and running for 360°O.D.

Peripheral indirect ophthalmoscopy in the left eye revealed a substantial vitreous hemorrhage centrally which obscured the optic nervehead and macular regions and most of the remaining retinal tissue proximal to the equator. A very dense and fresh-looking vitreous hemorrhage was observed overlying the peripheral retina and pars plana regions inferiorly O.S. A retinal sea fan was observed at the equator in the superotemporal quadrant. Although the vitreous hemorrhage was of moderate density, there was no evidence of any retinal tears or a retinal detachment at that time. A and B scan ultrasonography of the left eye revealed a diffuse vitreous hemorrhage, without any evidence of a retinal detachment O.S.

At this point, it was elected to observe the left eye and wait for possible clearing of the recent vitreous hemorrhage in the left eye. However, three weeks after the initial examination, the patient developed a rhegmatogenous retinal detachment (Fig. 1).

The patient was hospitalized at The Mount Sinai Medical Center, New York, and had 100° of scleral buckling surgery including a scleral bed dissection with cryopexy of the retinal tear (sea fan) and drainage of the subretinal fluid. A 360° encircling band was also positioned over the buckle site. The retina was reattached at the time of surgery and remained so postoperatively (Fig. 2). The scleral buckling surgery was carried out in the hyperbaric chamber at two atmospheres of pressure of oxygen.

The hyperbaric oxygen chamber at The Mount

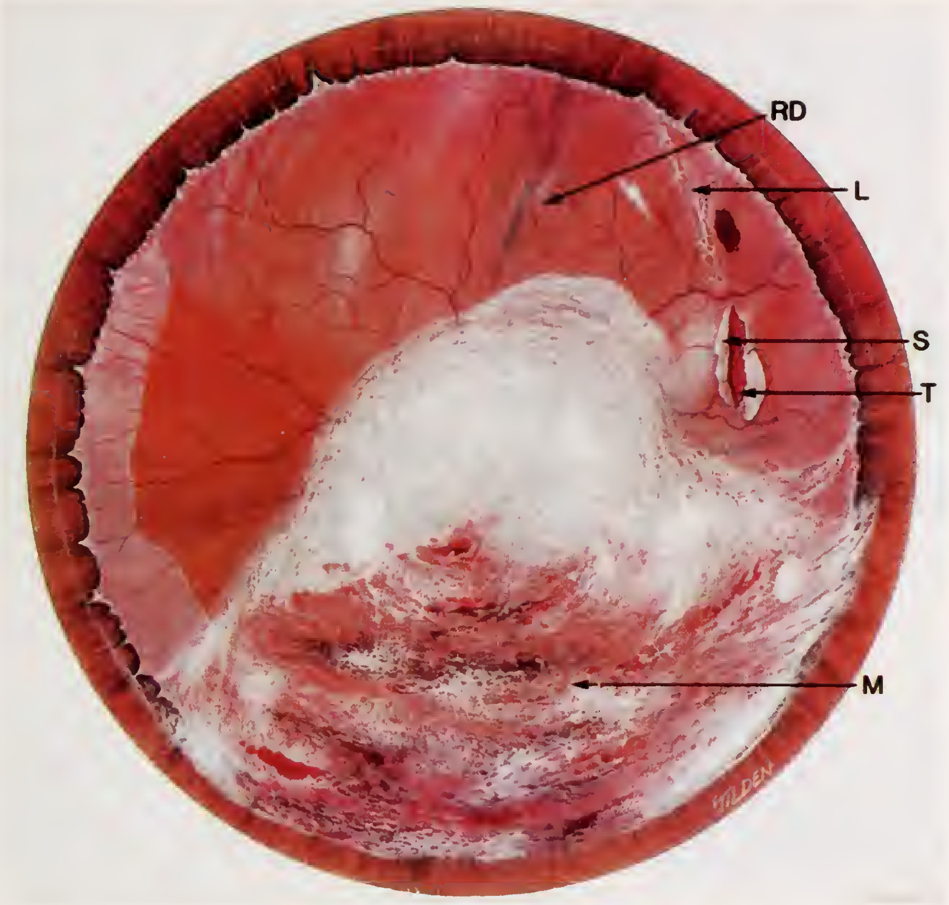

FIG. 1. Fundus drawing of the left eye of a patient with proliferative sickle retinopathy. An infarcted sea fan (S) (retinal arteriovenous shunt) is the site of a retinal tear (T). The latter is responsible for a retinal detachment (RD). A vitreous hemorrhage with vitreous membranes (M) is present obscuring the disc and macula regions in the posterior polar region of the eye. Lattice retinal degeneration (L) is also present.

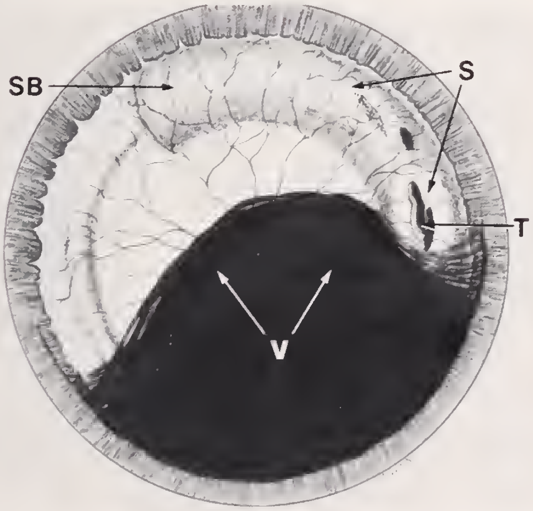

FIG. 2. Fundus drawing of the patient's left eye after scleral buckling surgery in the hyperbaric chamber and reattachment of the retina. Note the scleral buckle (SB). There are several zones of chorioretinal scarring (S) around the retinal tear (T) from the cryopexy surgery. The vitreous membrane (V) and hemorrhage remained.

Sinai Hospital in New York consists of two interconnected stainless steel lined chambers whose outer shape, with port windows, and overall sturdy construction is like the hull of a submarine. The chambers can be pressurized individually or together. The larger of the two chambers is a fully equipped operating room (Fig. 3). The pressure inside the hyperbaric chamber, once sealed, is regulated from the outside by an engineer. Communication between the operating staff inside the chamber and the staff outside the chamber is continuous using loudspeakers, telephones and closed circuit T.V. The controls outside the operating chamber are demonstrated in Fig. 4.

The patient was then brought into the hyperbaric operating chamber and all of the operating room personnel were scrubbed and gowned (asbestos material) prior to sealing the chamber. Then the pumps were started and the pressure within the chamber was gradually elevated to 2

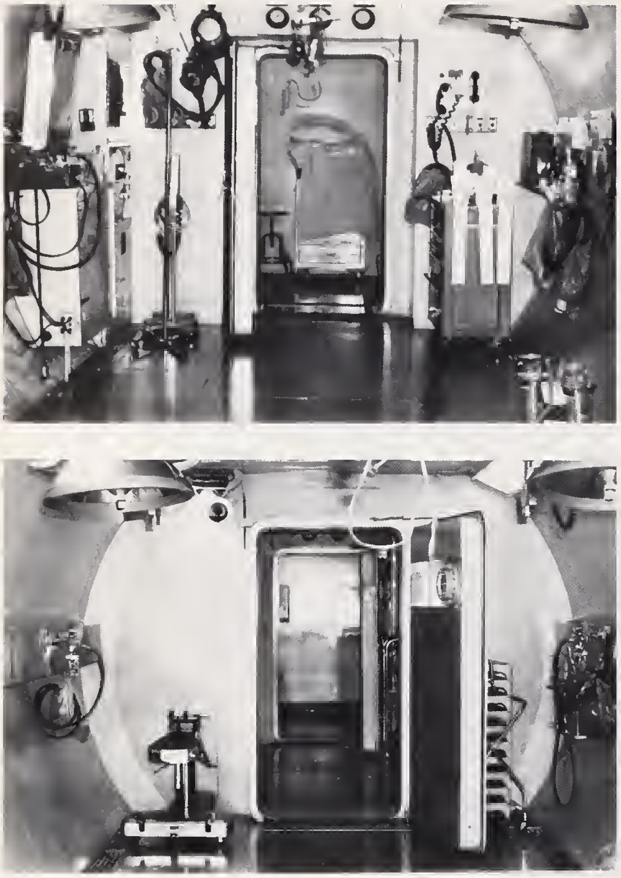

Fig. 3. Hyperbaric chamber at The Mount Sinai Medical Center. Upper—view of chamber from outside. Lower—view of chamber from inside. Note heavy air locked door that is open to the outside.

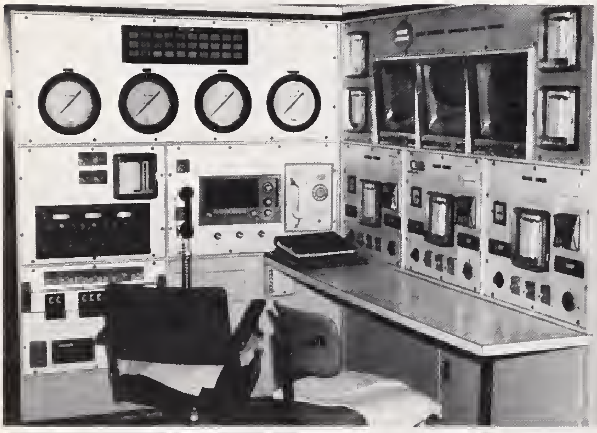

Fig. 4. Hyperbaric chamber control station outside the chamber which controls the atmospheric conditions during surgery and has telephone as well as closed circuit T.V. Communications with the operating staff inside the chamber.

Atm of oxygen prior to the induction of general anesthesia. This was done to allow the patient to swallow thereby equilibrating the pressure within the inner ear with the environment and eliminating the need for a possible myringotomy.

Once 2 Atm of pressure was reached, anesthesia was induced using only nonflammable anesthetics. All electrical connections within the chamber were bathed in nitrogen gas to prevent flash fires and all personnel wore special nonflammable gowns. All drapes used in the chamber were made of nonflammable material.

Because of the possibility of scleral necrosis and anterior segment ischemia a pars plana vitrectomy was deferred at the time of scleral buckling surgery. Three months later with the retina well attached, a pars plana vitrectomy (21–23) using the bimanual technique (24) was performed under general anesthesia and hyperoxygenation, at normal atmospheric conditions, with an excellent postoperative result (Fig. 5). The patient's best final corrected visual acuity was in the 20/40 range which was a significant improvement compared to the original preoperative vision of hand motion at one foot.

Discussion

Vitreous hemorrhages are not uncommon in sickle cell patients (25–27) with hemoglobin SC who have developed sea fans. Once this occurs vitreal membranes may evolve and develop vitreoretinal traction forces leading to either a tractional and/or a rhegmatogenous retinal detachment. Surgical attempts to correct retinal detachments in sickle cell patients have been poor compared to comparable retinal detachment repairs in non-sickle cell patients (8).

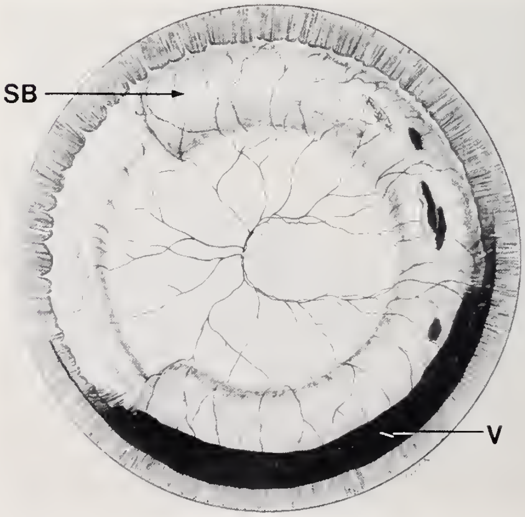

Fig. 5. Fundus drawing of patient after pars plana vitrectomy surgery under normal atmospheric conditions. Note the previous scleral buckle (SB). The vitreous hemorrhage and membranes have been removed centrally allowing an internal window within the eye for vision. The retina also remained attached. A zone of vitreous membrane (V) remains in the retinal periphery.

It is well established that sickle cell patients have a significantly higher potential for developing scleral necrosis, anterior segment ischemia and ultimately phthisis bulbi from conventional scleral buckling surgical techniques especially if heavy diathermy and/or cryosurgical treatment is performed (8–12). Use of hyperbaric oxygen (17–19) has been advocated to lessen the chances for sickling in those sickle cell patients undergoing scleral buckling surgery for repair of a retinal detachment.

However, it is possible to hypertransfuse the sickle cell patient with packed cells preoperatively as well as intraoperatively thereby obviating the need for a hyperbaric chamber (16). Also, with judicious use of diathermy and/or cryosurgical modalities, one can avoid the dreaded complications of retinal detachment surgery in patients with proliferative sickle retinopathy.

This case illustrates that staging the ocular surgery in a sickle cell patient who requires multiple procedures, for example, scleral buckle and pars plana vitrectomy surgery, may very well avoid the previously mentioned ocular complications. This in turn will allow for successful restoration of the globe so that it may serve visual functions once again.

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Neurologic-Neurosurgical Notes

Allan E. Rubenstein, M.D. and Martin H. Savitz, M.D., Coeditors

Primary Vertebral Tumor in an Adolescent Girl

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Dorothea Worcester, M.D., and Harvey M. Peck, M.D.

Abstract

A thirteen-year-old girl was admitted with a six-month history of low back pain, a palpable paravertebral mass, and a left third lumbar radiculopathy. Radiologic studies were consistent with a primary vertebral neoplasm. The differential diagnosis, the microscopic pathology, and a review of the world literature are discussed.

Introduction

Bone tumors seldom arise in the vertebral column. Once nonneoplastic conditions such as tuberculosis, hyperparathyroidism, and histiocytosis X have been ruled out, tumorous lesions of both a benign and malignant nature must be considered. In contrast to metastatic carcinoma of the spine which may necessitate decompressive laminectomy in adults, primary vertebral tumors in children are rarely seen in neurosurgical practice.

Case Report

A thirteen-year-old girl noted the onset of vague low back pain after exercising in her school gymnasium. There was little localization of her discomfort, and no relief unless she ceased weight-bearing and confined herself to bed. She had not experienced menarche, and her past medical, family, and social history were all noncontributory. Neurosurgical consultation was requested only after the child had been symptomatic for six months.

Physical examination revealed marked left paravertebral spasm in the lumbosacral area. With the patient prone, a firm, nontender mass about 6 cm in diameter could be palpated immediately to the left of the second, third, and fourth lumbar spinous processes. Neurologic examination demonstrated hypesthesia in the left third lumbar dermatome, a decreased left patellar reflex, and weakness of the left quadriceps femoris. Electromyography confirmed left third lumbar radiculopathy.

X-rays (Fig. 1) showed absence of the left transverse process of the third lumbar vertebra, erosion of the pedicle, and enlargement of the foramen, consistent with a neurofibroma. Computerized axial tomography (Fig. 2a, 2b) revealed a destructive lesion involving half of the vertebral body, expanding into the psoas muscle, and displacing the kidney and ureter. Lumbar myelography (Fig. 3) demonstrated encroachment on the dural contents. Abdominal aortography (Fig. 4) showed a hypervascular mass fed by the third lumbar artery; the venous phase showed the tumor stain as well as a nonobstructed pyelogram.

A laminectomy was performed to decompress the neural elements and obtain a biopsy. The

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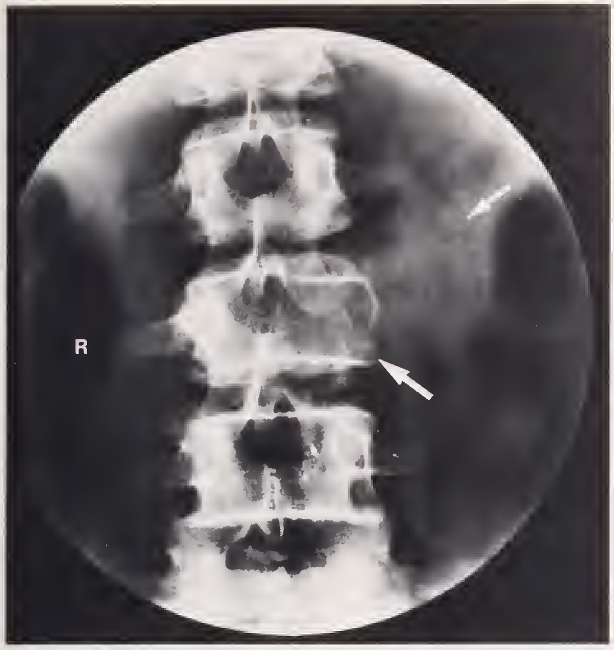

FIG. 1. Radiograph of lumbar spine. Note loss of substance in L3 vertebral body (lower arrow), including loss of trabecular pattern, dimunition in height, and absence of left transverse process. A soft tissue mass lies adjacent to spine and bulges psoas margin laterally (upper arrow).

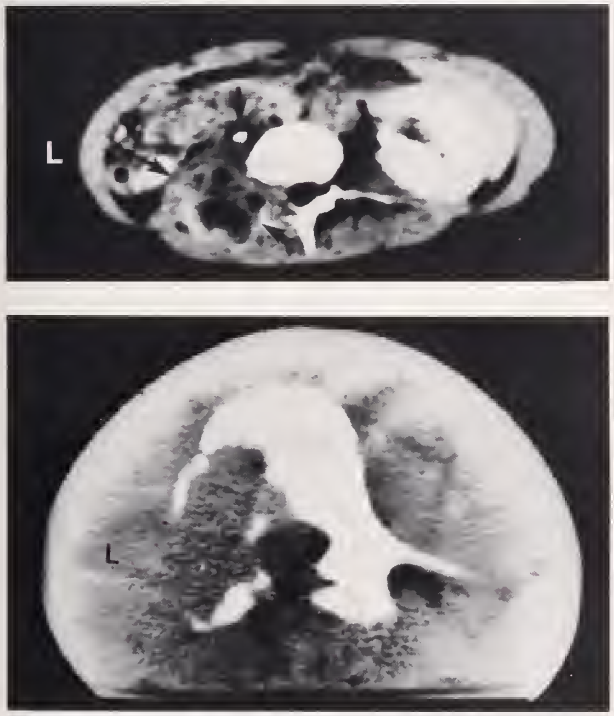

FIG. 2a. Computerized axial tomography through the level of L3 vertebral body with contrast material shows a large left paraspinal mass (oblique arrows) associated with loss of bony substance on left side of neural arch. Multiple cystic areas are seen within the soft tissue mass. The ureter (vertical arrow) is displaced anteriorly, but not obstructed. Fig. 2b. High magnification with thin slice technique reveals the irregular loss of bone on the left side of vertebral body and appendages.

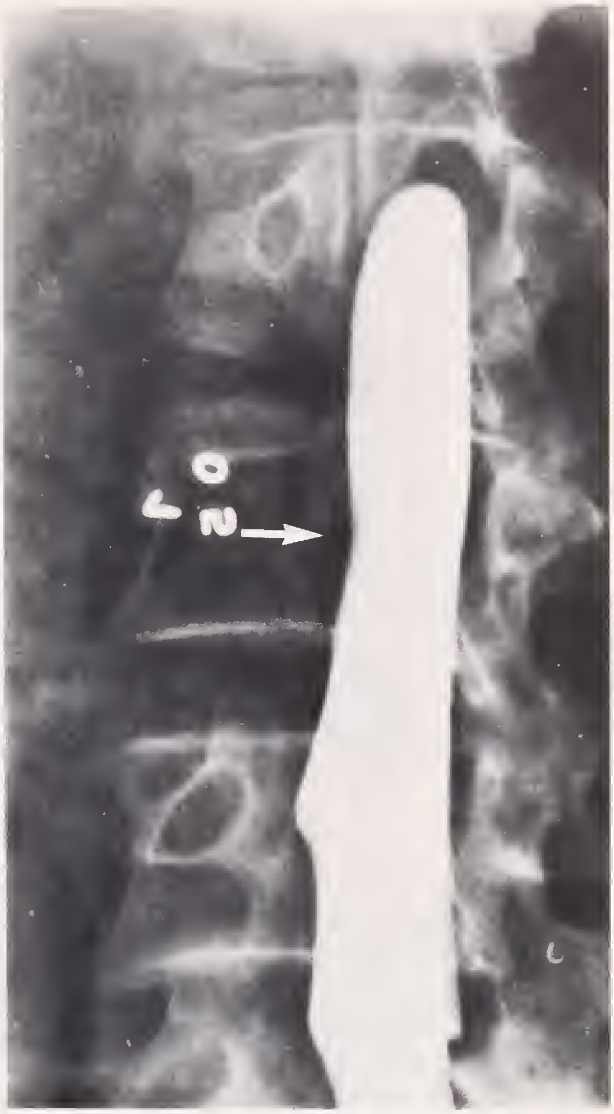

FIG. 3. Myelography with ethyl iodophenylundecylate. Note compressive effect on left aspect of opaque column (arrow). Absence of the pedicle is also apparent.

preoperative diagnosis was osteosarcoma. At surgery, the mass was readily identified as it extended into the paravertebral musculature. Part of the tumor was resected from muscle, but no clear plane was found. The left hemilamina and facet joint were invaded by neoplasm. The dura was noted to be pulsing normally at the end of the procedure.

The tissue sections (Fig. 5) revealed a solid vascular tumor with multinucleated giant cells, areas of foamy histiocytes with hemosederin, and many osteoblasts. No mitosis was observed. The microscopic findings were consistent with benign osteoblastoma.

Postoperatively, the patient became free of pain. Eight weeks later following phlebotomy for autotransfusion, the mass lesion was totally ex-

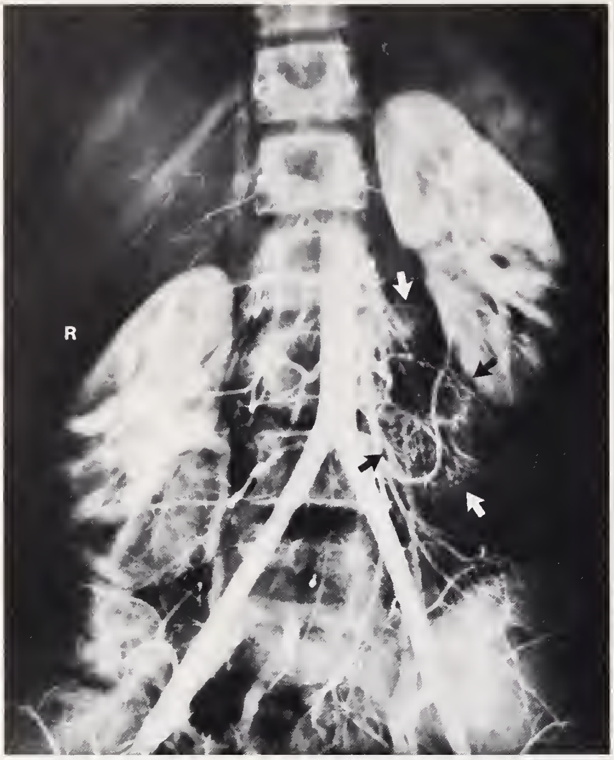

FIG. 4. Midarterial phase of flush aortogram shows a hypervascular left paraspinal mass (between arrows).

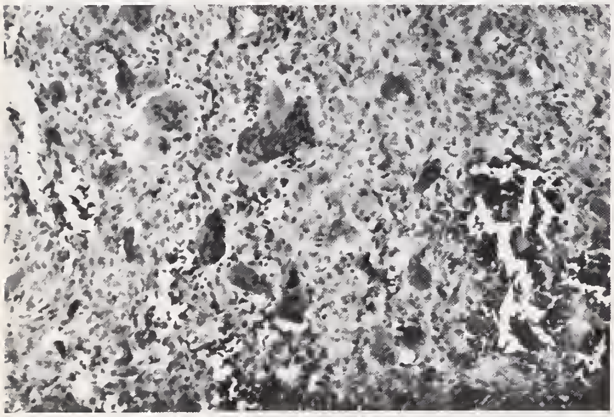

FIG. 5. Original biopsy specimen. Note many multinucleated giant cells, small vascular spaces (arrows), and a stroma of osteoblasts and histiocytes containing hemosiderin (H&E ×10).

cised through a left lumbar oblique incision by combined neurosurgical, orthopaedic, and general surgical techniques. A definite capsule was found, and the kidney and ureter were easily separated. After the bulk of the tumor had been amputated from the vertebral body, the remaining neoplasm was removed by curettage. Grafts were then obtained from the iliac crest and the sixth rib. The defect left by hemivertebrectomy was filled with bone from the ilium. The rib was fashioned into an extravertebral strut extending from the second to the fourth lumbar levels (Fig. 6). During the period of spinal fusion, she was maintained in a plastic molded pelvicothoracic brace.

The gross specimen (Fig. 7) was 8 cm in its greatest diameter and weighed 65 gm; dissection revealed multiple cavernous areas filled with blood and consistent with an aneurysmal bone cyst. On stained sections (Fig. 8), the capsule is

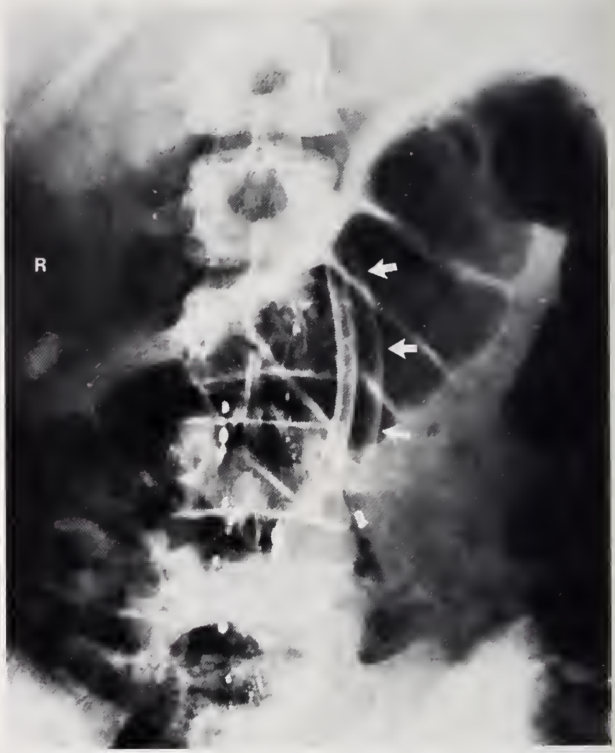

FIG. 6. Postoperative x-ray shows the rib strut graft (arrows), stretching from transverse process of L2 to L4, bypassing and supporting the destroyed portion of L3 vertebra.

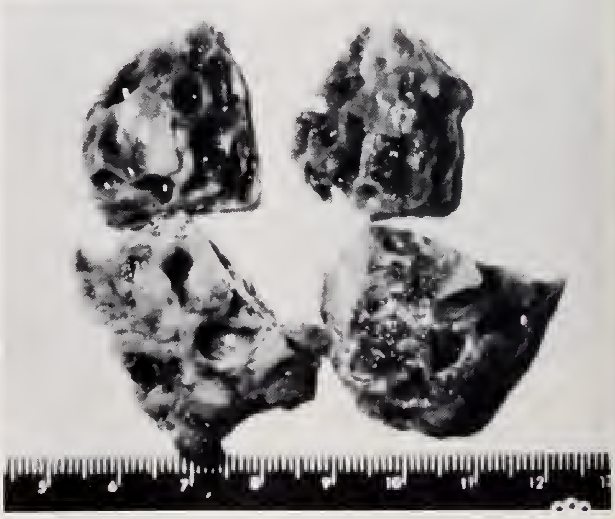

FIG. 7. Cross section of gross specimen demonstrating encapsulation and multivascular honeycombed channels.

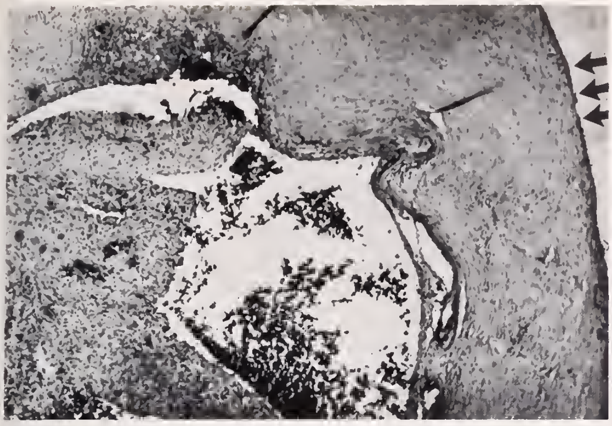

FIG. 8. Low power view demonstrates capsular wall (arrows), composed of fibrous tissue. In the center, a large vascular sinus is lined by elongated cells. (H&E ×2.5).

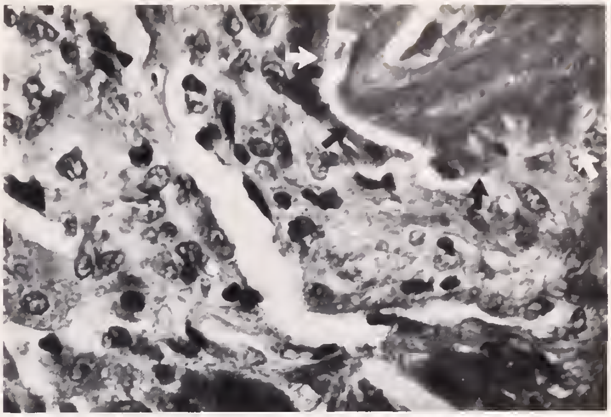

FIG. 10. An area of osteoid formation (arrows) in another part of the tumor (H&E ×40).

clearly identified; the wall has a zone of fibroblasts and fibrocytes. The sinusoids are mostly lined by flattened cells but also by some rounded cells resembling osteoblasts. The stroma adjacent to the sinusoids (Fig. 9) is more cellular as already seen in the biopsy material. In another area (Fig. 10), new bone formation is seen.

Three months after surgery, x-rays confirmed spinal fusion to be complete. Two years later, there is no evidence of recurrence. The patient has begun normal menstrual cycles. She is fully able to participate in the activities of daily living and engages in sports activity regularly.

Discussion

A total of 296 cases of aneurysmal bone cyst were collected from the world literature (1–4); 21 percent occurred in the vertebral column, and the lumbar segments were most often involved. About 70 percent were reported in the first two decades, but the sex distribution was not accurately recorded. A total of 245 cases of benign osteoblastoma were collected from the world literature (4–8); 30 percent occurred in the vertebral column, and the lumbar segments were most often involved. About 60 percent were reported in the first two decades, and 65 percent were recorded in males.

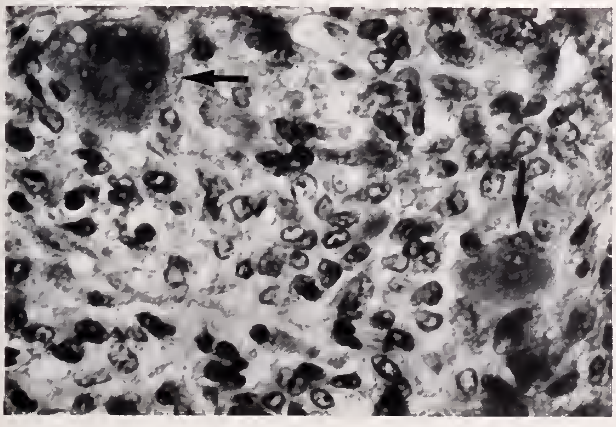

FIG. 9. High power view of giant cells (arrows) and stroma of precursor cells. (H&E ×40).

The pain associated with osteoblastoma is insidious in onset and sufficiently mild so that the delay before seeking medical attention averages many months. The aching discomfort is not responsive to salicylate therapy in the dramatic fashion that characterizes osteoid osteoma. A localized, tender, palpable mass is more likely to be found in cases of benign osteoblastoma than in intramedullary osteoid osteoma. Although scoliosis may be present when either tumor arises in the spine, 60 percent of the patients with benign osteoblastoma had demonstrable motor or sensory deficits on neurological examination.

The vascular, cellular, and osteogenic characteristics of this case suggest a high degree of histologic pleomorphism. With the predominant vascular elements being sinusoidal, the distinction from aneurysmal bone cyst becomes difficult if not impossible. In his text on bone tumors, Dahlin (5) comments that there is enough overlap of clinical and histopathologic features to suggest a relationship between aneurysmal bone cyst and osteoblastoma. The lack of distorted nuclei or bizarre giant cells rules out any malignant change; however, transformation of a benign osteoblastoma to an osteogenic sarcoma has been described in one patient (9).

Total surgical excision was decided upon after biopsy because of reports of agressive osteoblastomas which exhibit a propensity for destructive local growth without restraint although metastasis has never been documented. Less extensive removal and simple curettage have arrested some osteoblastomas (5). In a series collected by Marsh, Bomfiglio, and Enneking (7), the recurrence rate was about 10 percent. Radiation therapy has had no effect on the rate of recurrence, and one case of postradiation fibrosarcoma has been reported in a lesion involving the spine (5).

Primary vertebral tumors may present with neurologic symptoms and signs in children. Computerized axial tomography in conjunction with myelography and angiography establishes the extent of the neoplasm if not the actual diagnosis. Combined neurosurgical, orthopaedic, and general surgical techniques allow complete removal of even extensive benign lesions.

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Student's Corner

Benjamin Hoffman, B.A., Editor

Evaluation of CPR Performance among Medical Students, Residents, and Attendings at Mount Sinai School of Medicine

Marc Nelson, B.A.*

Abstract

Medical students, residents and faculty members at Mount Sinai School of Medicine were evaluated in their performance of cardiopulmonary resuscitation (CPR). Both cognitive and psychomotor skills were tested. There was a significant discrepancy between theoretical knowledge and actual performance. Of the 138 people tested, only 4 (2.9 percent) performed CPR better than the minimum level required to be certified by either the American Heart Association (AHA) or the American Red Cross (ARC).

Introduction

Each year more than 750,000 Americans die from cardiac arrest (1). Many of these deaths occur within a hospital. Without resuscitation, cardiac arrest invariably leads to death. The crucial time for resuscitation is the first five minutes. (2, 3) Properly performed CPR can greatly reduce morbidity and mortality; however, even with correct technique, stroke volume is reduced to only 30 percent of normal. With incorrect technique, CPR can be virtually useless.

Practically all members of the medical community will at one time in their career be called upon to perform CPR. Many will perform it numerous times (4). Yet, many victims would be better off if CPR were performed by a trained layperson rather than by a doctor (5).

Several methods of instruction have been formulated to train people in CPR ranging from short demonstrations to approved AHA or ARC courses. This study was not designed to compare the different methods, but rather to assess, regardless of training, the general level of performance in one hospital community.

Materials and Methods

Subjects for the study included third- and fourth-year medical students, residents and attendings at The Mount Sinai Hospital and Elmhurst General Hospital, a Mount Sinai affiliate. Approximately one-third of the subjects asked to participate declined after being told the nature of the study.

A two-part exam was given with the practical portion of the test being given first to avoid refreshing anyone's memory.

The practical exam consisted of 12 items which were evaluated by observation and data from a Recording Resusci Annie manikin's printout tape. The first eight items assess the ability of the rescuer to establish that cardiac arrest has occurred and to correctly prepare and position the victim for the administration of CPR. The seventh item (removing the shirt) is usually neglected in CPR

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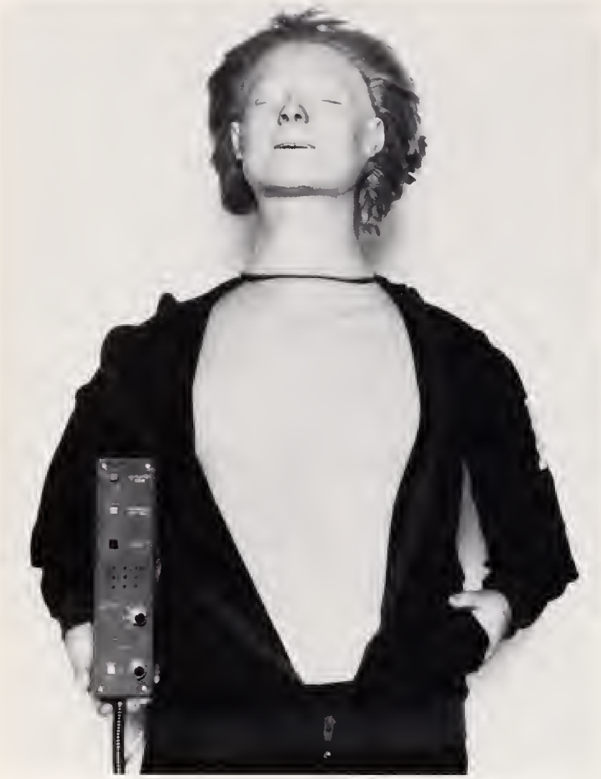


FIG. 1. Recording Resusci Annie

FIG. 2. Close-up of chest showing recording box. Top light indicates adequate ventilation (over 800 cc). Middle light indicates depth of compression. Bottom light indicates incorrect hand position.

courses, yet incorrect hand position is a frequent problem and removal of the shirt not only facilitates initially finding the correct spot for compressions, but also makes it easier to return after ventilating as there is a red mark on the chest.

The remaining four items, which were recorded by the manikin, measured the actual performance of CPR.

The second portion of the exam was a written test consisting of 25 multiple-choice questions. The questions tested five basic areas of knowledge: recognition (two questions), airway (four questions), artificial respiration (four questions), compressions (seven questions), ventilation/compression ratio (two questions), and obstructed airway (six questions).

Evaluation

Although the purpose of this study was to determine the level of competence regardless of training, participants were nonetheless separated into groups based on the presence or absence of prior training.

To meet the recommended AHA or ARC standards (6), all items on the practical exam with the exception of number 7 had to be performed correctly.

CPR performance was evaluated solely on the basis of the tapes recorded by the manikin, which was checked after each test to make sure it was not malfunctioning. The tapes not only provide an objective measurement of performance but also permit one to determine exactly what mistakes are being made.

Discussion

The results (Tables I, II, and III) are at best pitiful. Only four out of 138 people tested, 2.9 percent, performed CPR at an acceptable level.

The most common sources of error were compressing too vigorously and failure to adequately

TABLE I
Practical Test

	Previous Training (93)						No Prior Training (45)					
	Yes			No			Yes			No		
	M*	R*	A*	M	R	A	M	R	A	M	R	A
1. Established unresponsiveness	25	34	14	6	7	7	10	7	5	9	4	10
2. Opened airway	10	18	8	21	23	13	1	3	3	18	8	12
3. Established respiratory arrest	12	15	11	19	26	10	1	2	3	18	9	12
4. Initiated respiration with 4 quick breaths	14	8	2	17	33	19	1	0	0	18	11	15
5. Checked pulse	10	25	14	21	16	7	3	4	3	16	7	12
6. Used carotid artery for above	8	20	11	23	21	10	0	2	2	19	9	13
7. Removed shirt before beginning	7	12	4	24	29	17	4	4	4	15	7	11
8. Correct hand position	6	8	2	25	33	19	0	1	2	19	10	13
9. 60 or more compressions per minute	24	25	12	7	16	9	3	6	4	16	5	11
10. Correct compressions	2	3	0	29	38	21	0	0	0	19	11	15
11. Incorrect compressions**												
A. Too light	3	12	3				6	2	3			
B. Too hard	20	22	12				9	8	10			
C. Inadequate release	6	4	6				4	1	2			
12. 8 or more breaths	4	10	12	27	31	9	3	4	2	16	7	13
13. 8 breaths > 800 cc	1	4	3	30	37	18	1	0	0	18	11	15

* M—Medical Student
R—Resident
A—Attending

** Participants with mistakes in more than one category were placed in the category in which they made the most errors.

TABLE II
Written Test

	Previously Trained		No Prior Training	
	Pass	Fail	Pass	Fail
Medical Students	27	4	4	15
Residents	35	6	5	6
Attendings	18	3	10	5
TOTAL	80 (86%)	13 (14%)	19 (42%)	26 (58%)

TABLE III
Total Performance

	Previously Trained		No Prior Training	
	Pass	Fail	Pass	Fail
Medical Students	1	30	0	19
Residents	3	38	0	11
Attendings	0	21	0	15
TOTAL	4	93	0	45

tilt the head while giving artificial respiration resulting in inadequate or no ventilation.

Evident also, was a large discrepancy between cognitive and motor skills. This may be caused, in part, by the many courses, especially "in-house" courses, that just show films and give demonstrations, while allowing minimal or no time at all to practice on manikins.

One of the more shocking aspects of the study is that although 78 percent of the people tested felt confident in their ability to perform CPR (Table IV), only 2.9 percent did it correctly. This is unfor-

TABLE IV

Confidence in One's Ability to Give CPR

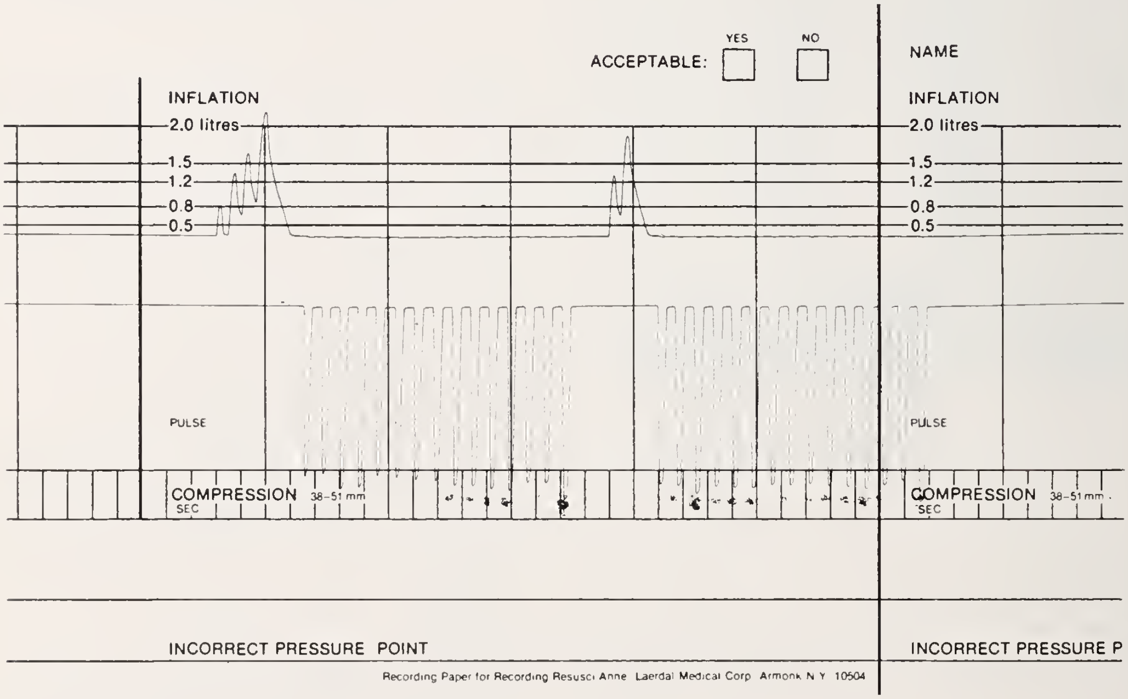
	Feel Confident	Do Not Feel Confident
Medical Students	34	16
Residents	48	4
Attendings	25	11
TOTAL	107 (78%)	31 (22%)

TABLE V

	Performed CPR	Never Given CPR
Medical Students	24	26
Residents	46	6
Attendings	32	4
TOTAL	102 (74%)	36 (26%)

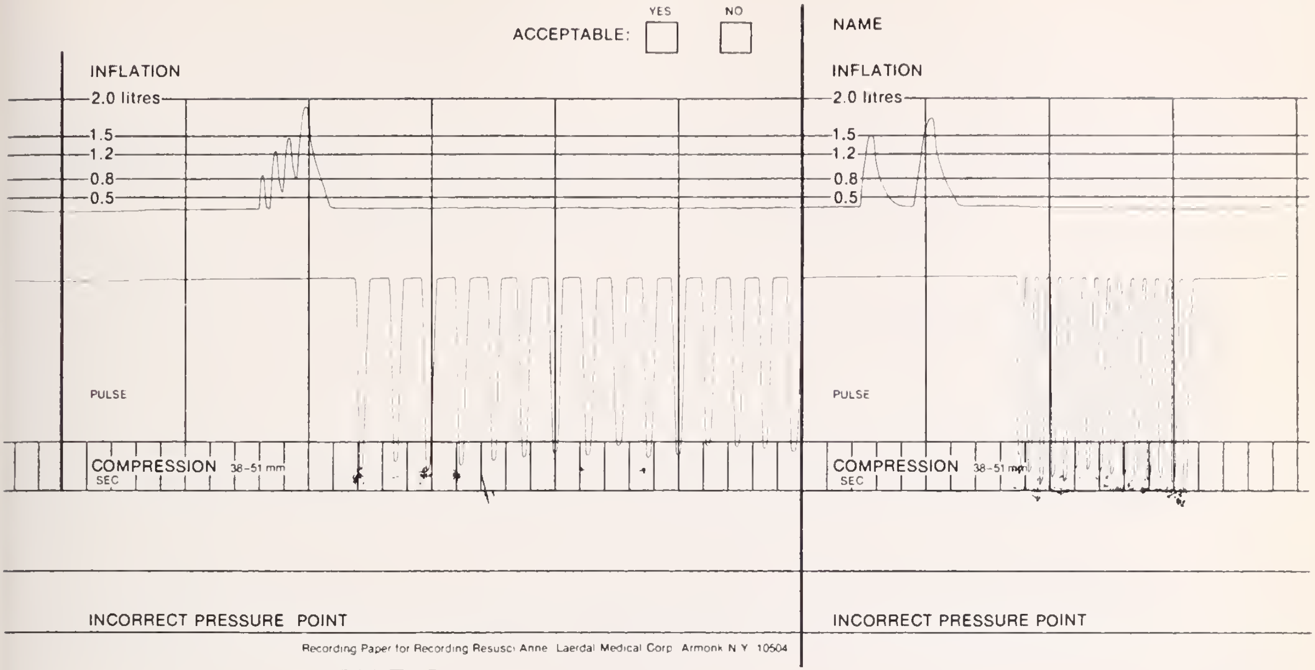
tunate as these people are unlikely to feel a need for additional training or for refresher courses. This large discrepancy between imagined and actual ability probably results from the assumption that because they know what to do (and in fact over 70 percent did pass the written test) they are qualified to do it. However, this is no truer in CPR than it is in surgery or anything demanding a high degree of technical skill.

Although there are a few possible sources of error in this study, these would, for the most part, tend to give greater credence to the results. For example, the study group was not well randomized. As previously stated nearly one-third of those asked to participate refused. However, the great majority of them gave lack of knowledge as the reason for refusing. Also, tapes were only run for approximately one minute—most people tend to deteriorate after a few minutes. In addition, they were only tested on one-rescuer CPR and not on the more complicated two-rescuer CPR. However, it must also be noted that some people did not take the test entirely seriously and under real conditions they may have performed better. Of course, under the stress of a real cardiac arrest many may also have performed worse.



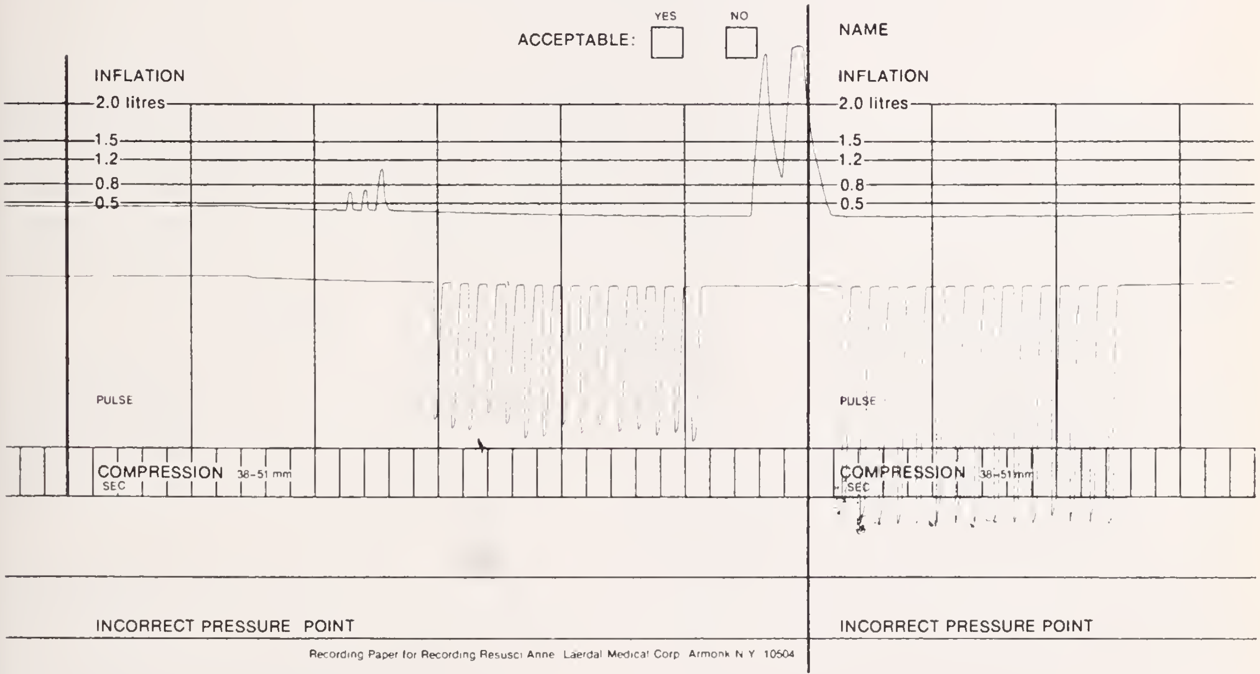
TAPE I

I. Correct CPR
  A. Ventilation
    1. Four quick breaths (0.8 l., 1.3 l., 1.6 l., and 2.1 l. respectively)—good
    2. Second two breaths—adequate amount of air (>800 cc)
    —appropriate amount of time taken to give them (<5 seconds)
  B. Compressions
    1. Rate—good (80/mn)
    2. Depth—good (between 31 and 51 mm)



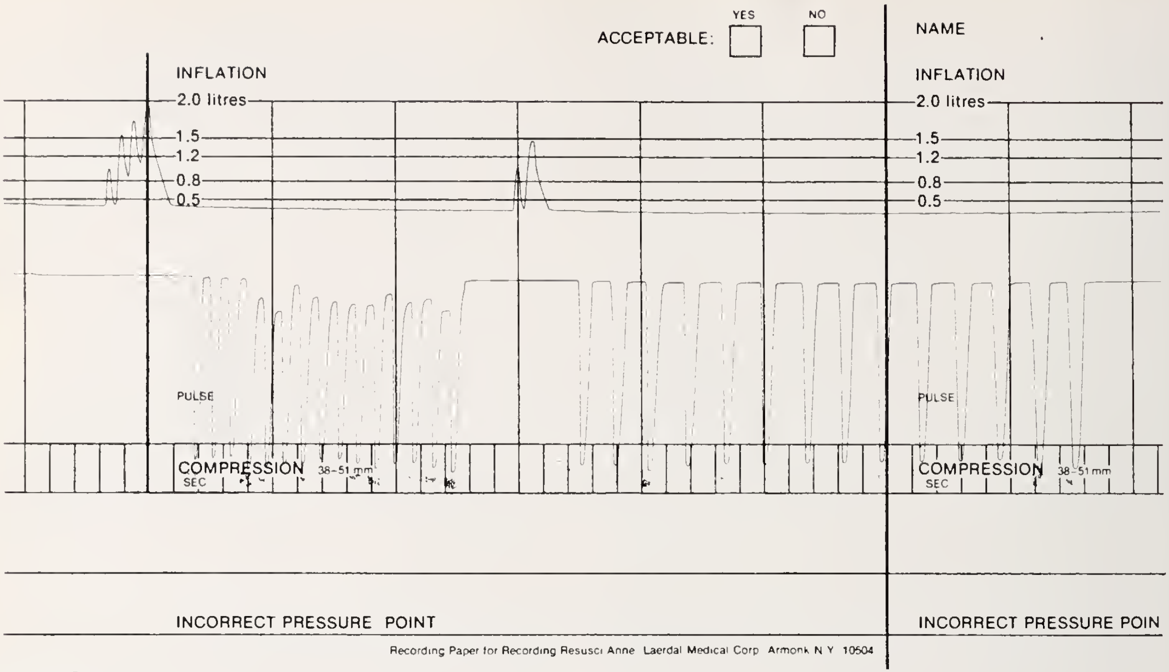
TAPE II

II. Incorrect CPR
  A. Ventilations
    1. Four quick breaths—good
    2. Second two breaths—too slow
  B. Compressions
    1. First set—depth good, but rate too slow (48/mn)
    2. Second set—depth good, but rate too fast (120/mn)



TAPE III

III. Incorrect CPR
  A. Ventilations
    1. Four quick breaths—inadequate amount of air
    2. Second two breaths—too powerful and too slow
  B. Compressions
    1. First set—rate good, but depth inadequate (30–36 mm)
    2. Second set—rate good, but depth too great (55–60 mm)



TAPE IV

IV. Incorrect CPR
- A. Ventilations
  - 1. Four quick breaths—good
  - 2. Second two breaths—good
- B. Compressions
  - 1. First set—inadequate release (which means that the heart does not have the chance to expand and thus refill in between compressions)
  - 2. Second set—depth good, but rate too slow (42/mn)

Recommendations

New York state law now requires that all house staff be certified in CPR and numerous courses have been devised to help meet this goal. The emphasis in these courses must be directed toward attaining the practical skills necessary to perform CPR. The theory can be read.

All courses should be taught with Recording Resusci Annies. Although this entails incurring a significant increase in cost (each manikin costs approximately $1,000), it is necessary for effective instruction. With this device, the person being trained in CPR can receive immediate quantitative feedback, as well as reinforcement on the adequacy of his technique. It also removes the subjective aspect in assessing whether or not the student is performing satisfactorily. Finally, when used as a screening tool to "spot check" and evaluate CPR performance, it demonstrates to the person being tested in an unequivocal manner how well he or she performs CPR.

CPR skills tend to deteriorate (5). It is possible that at one time many of those tested performed quite well. Optimally, annual refresher courses should be given and should be mandatory. At the very least, recording manikins should be readily available so that anyone wishing to use one may conveniently refresh the skills needed.

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The Effect of Insulin on the Exocrine Pancreas: A Review

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Abstract

Examination of the various animal models of diabetes mellitus demonstrated that pancreatic acinar enzyme and volume outputs are reduced and histologic defects of the acinar pancreas may be observed with light and electron microscopy. Insulin increased glucose uptake and had some reparative effects on the pancreatic acinar cells of these diabetic animals. These data demonstrated that induced diabetes mellitus had physiologic and morphologic effects on the exocrine pancreas. The morphologic component might be comparable to human pancreatitis and insulin had a partial reparative effect. In the studies in which a hyperglycemia was induced in normal animals, mimicking one aspect of diabetes mellitus, there might be an increase or a reduction in pancreatic enzymes but the electron microscopic appearance of the pancreatic acinar tissue was not altered. The lack of a uniform physiologic response to the induced hyperglycemia might be explained in part by: varied concentrations of glucose administered, varied rates of glucose administration, varied routes of glucose administration, possible alteration of pancreatic blood flow, possible release of serotonin, possible release of antidiuretic hormone and a possible gastric effect which decreased the passage of acid into the duodenum but augmented the release of gastrin. In man, diabetes mellitus resulted in atrophy of the pancreas with interacinar fibrosis and interstitial pancreatitis. The mechanism by which diabetes mellitus induced these structural changes in the pancreatic acinar cells has not been determined. However, the exocrine pancreas is just one of a number of systems altered by the generalized metabolic disturbance of diabetes mellitus. This degree of morphologic change in the exocrine pancreas might be the reason for the varied physiologic observations that either showed no change or a depression of pancreatic function. The depressed pancreatic exocrine secretion of diabetes mellitus, that could be modified by insulin, is comparable to the reduced pancreatic exocrine flow observed in pancreatitis. The varied pancreatic exocrine secretion might also have been the result of a paradoxical gastric effect. The gastric secretion of patients with diabetes mellitus is reduced and there is less acid entering the duodenum to activate the secretin-pancreozymin mechanisms. However, the reduced gastric stasis of these patients might also cause an augmented release of gastrin which stimulates the acinar pancreas. The administration of glucose to man is subject to the same variables noted in animals, for the hyperglycemic effect had no pancreatic exocrine effect in some studies, though in most of the studies the pancreatic volume and enzymes were depressed.

No animal models for hyperinsulinism could be identified, but in man hyperinsulinism resulted in ductal and centroacinar hyperplasia and an increase in pancreatic fat and connective tissue. In the studies in which insulin-induced hypoglycemia were carried out, mimicking one aspect of hyperinsulinism, the pancreatic exocrine secretion in animals and man were usually augmented. Insulin-induced hypoglycemia stimulated the vagus nerves and augmented the activities of the exocrine pancreas by: augmented gastric acid secretion which passed into the duodenum and released secretin and pancreozymin, increased release of gastrin, increased sensitivity of the exocrine pancreas to secretin, and directly stimulating the exocrine pancreas.

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Introduction

The exocrine part of the pancreas is adapted for the synthesis and secretion of digestive enzymes. The mechanism for this secretion of pancreatic juice has been the subject of extensive studies. Pavlov and his associates (1) demonstrated the significance of the nervous mechanism and the regulation of the pancreatic exocrine secretion was clarified in some degree by the discovery of secretin (2) and pancreozymin (3). Microscopic studies (4) have long since shown that the exocrine cells of the pancreas contain characteristic granules that decrease when the pancreatic secretion is stimulated and the digestive enzymes are discharged into the intestines. However, our knowledge concerning the mechanisms for the discharge of the secretion and the synthesis of the enzymes is still imperfect. This review is an attempt to summarize the current information available on this subject for the actions of the hormone insulin.

The Effect of Diabetes Mellitus on the Exocrine Pancreas

Ever since the discovery by von Mering and Minkowski (5) that extirpation of the pancreas in the dog produced a condition closely resembling diabetes mellitus in man, reports appeared in the literature implicating the external secretion of the pancreas in this condition. In the intervening years, much evidence has accumulated that indicates that the acinar tissue and presumably its product, pancreatic juice, played no role in pancreatic diabetes but that this condition was caused by partial or complete insufficiency of the beta cell of islet tissue. However, the question was soon raised on the possible role of islet tissue on the acinar pancreas. What would happen to pancreatic acinar tissue with diseased islet tissue or more specifically with diseased beta islet cells? There is no morphologic proof to separate the islet tissue, as an organ of internal secretion, from the rest of the pancreas (6, 7). There is histologic evidence that the islet tissue is incompletely separated from the acinar tissue (8) and that the arterial supply to and the venous drainage from these structures are not separate (6). There is also histologic evidence from adult pancreas that new formations of islet tissue may occur by transformation and hyperplasia of acinar, centroacinar or duct cells (9).

Diabetes Mellitus in Animals

There are a number of techniques available to study the effects of diabetes mellitus on the exocrine pancreas. Animals can be made diabetic by injections of alloxan or streptozotocin or genetically diabetic strains can be used.

No significant difference was noted in the pancreatic scan using (75) Se-Selenomethionine between normal mice and mice made diabetic with alloxan (10). In the mouse pancreas (35), S-methionine has been shown to penetrate more readily into perinsular acinar cells than into cells more remote from the islets (11).

In rats made diabetic by injections of alloxan, the pancreas was removed, homogenized and analyzed for enzymes. Pancreatic lipase, trypsin and chymotrypsin (12) were unaltered while in other reports (13) pancreatic trypsinogen, chymotrypsinogen and amylase (12–15) were reduced. Injections of insulin into these diabetic rats reversed the amylase depression (14, 15). It was postulated that insulin controls the biosynthesis of amylase by increasing the entry of glucose into the acinar cells (15). Insulin treatment of severely diabetic, nonketotic rats caused, after 90 minutes, a significant increase in pancreatic amylase activity with no change in other exocrine enzyme activities (13). A decrease in all pancreatic enzyme activities six hours after insulin was the result of an enhanced enzyme secretion (13). It was believed that insulin regulates pancreatic amylase synthesis mainly at the level of transcription (13). However, insulin plays only a permissive role in pancreatic amylase synthesis and is probably not involved in the short-term regulation of amylase synthesis in the nondiabetic state (13). In other studies in which rats were made diabetic with alloxan (16–18), it was observed that the pancreatic function depended upon the severity of the diabetes and was related to circulating insulin levels, for rats with high blood sugar and low insulin concentrations showed a disappearance of amylase from the exocrine pancreas and a depression of protein synthesis (16). Histologic analysis of the pancreas of rats made diabetic with alloxan (17, 18) revealed that the periinsular acini lost their typical characteristics and these cells become smaller, lost their refractiveness to the action of pilocarpine and had a decreased number of zymogen granules (17). Further, these pancreatic acinar cells showed group vacuoles, irregular granules whose density was not uniform and a disorder of the rough endoplasmic reticulum (18).

When rats were made diabetic by streptozotocin, a rapid degranulation of the beta islet cells was observed with destruction of the pancreatic acinar cells (19, 20). The acinar cells exhibited an irregular thickening of the endoplasmic reticulum with separation of lamellae, nuclear pyknosis, the mitochondria were poorly outlined with apparent degeneration of the cristae, the Golgi apparatus was atrophied, vacuolization of the cytoplasm was present, and the zymogen granules were immature (19, 20). One hour after an injection of insulin, the rough endoplasmic reticulum was activated and many intracisternal granules appeared (20). After regular injections of insulin, the rough endoplasmic reticulum showed regular arrangements, there was much less vacuolization, and fewer immature zymogen granules (20). Insulin appeared to have a reparative effect on the damaged acinar cells of diabetic rats. In addition, the streptozotocin caused a depression of pancreatic amylase activity and an augmentation of pancreatic lipase, trypsinogen and chymotrypsinogen (19). It appeared that the exocrine pancreatic dysfunction in diabetic rats was caused by the lack of the trophic effect of insulin on the acinar cells, particularly those surrounding the islet tissue.

In diabetic guinea pigs (21), there was a decrease in pancreatic volume, bicarbonate, and the enzymes amylase, trypsin and lipase to the intravenous infusion of secretin and cholecystokinin. Histologically, these diabetic guinea pigs exhibited total degranulation and fatty degeneration of the acinar cells. The degree of morphologic damage to the acinar pancreas altered the pancreatic secretion, with marked damage resulting in a sharp decrease in pancreatic secretion and little injury causing no alterations in the pancreatic juice outflow. Insulin also had a trophic effect on the guinea pig pancreatic acinar cells.

In studies on diabetic dogs induced with alloxan, it was noted that the threshold pancreatic exocrine response to secretin was increased four to twenty fold while the amylase concentrations were normal (22). Finally, when dogs received daily injections of a diabetogenic crude extract of ox anterior pituitary gland (23), a subacute pancreatitis was reported. The pancreatic acinar tissue showed small areas of necrosis and hemorrhage with inflammation of the interlobular connective tissue and fatty infiltration of duct epithelium. However, there was no extensive degeneration of the acinar epithelium and the stages of zymogenesis could be detected.

Diabetes Mellitus in Man

As early as 1884, it was observed that a considerable thickening of the walls of the arteries and arterioles occurred in the pancreas of diabetic patients (24). A series of postmortem studies were carried out on patients with diabetes mellitus in an attempt to correlate the islet tissue disease with possible pathology of the exocrine pancreas. The earliest studies were carried out on diabetes mellitus patients who died before insulin came into general use (25–27). Microscopically, interstitial pancreatitis (25, 26) was observed in 73% of the necropsy material, atrophy of the acinar tissue (26, 28, 29) was present in 54% of the cases, and fatty changes and fibrosis occurred in patients with diabetes of long duration. In the diabetic pancreas, there could also be found hyalinization of pancreatic tissue (27) as well as foci of fatty changes with sclerosis alternating with atrophy (29). The number of diabetic patients with interstitial pancreatitis sharply increased after the fourth decade of life (25, 26). In later studies, necropsy material was obtained from diabetic patients who had been treated with insulin (30–37). A comparison of the postmortem pancreas of 50 maturity onset diabetes with 50 nondiabetics revealed interacinar fibrosis, atrophy and arteriosclerosis in the exocrine pancreas of the diabetics (30, 32). Interacinar fibrosis in patients with diabetes mellitus has also been reported (31–34, 37). Other postmortem examinations of the pancreas of diabetics revealed pancreatic atrophy (34, 35, 37), the presence of a greater number of arteriolar lesions in the exocrine pancreas (33, 35, 36) and fatty infiltration of the pancreas (37). Further, the pancreas of diabetic patients tended to increase in size with age while the nondiabetic pancreas had a tendency to decrease with age (35). In juvenile-onset diabetes the pancreas was atrophic and infiltrated with fat (38) and inflammatory infiltrates were observed in and around the islet tissue (39). Whereas the exact cause of the exocrine pancreatic dysfunction in diabetes mellitus is not known, it has been suggested that repeated episodes of infarction with subsequent fibrosis may produce progressive destruction of islet and acinar tissue though the evidence for this is limited (32). It appears possible that the exocrine dysfunction might be related at least in part to the progressive structural damage of the diabetic pancreas and insulin therapy might not modify the course of these changes.

Studies have also been carried out on the pancreatic exocrine function of patients with diabetes mellitus. In one of the earliest studies (40) on an unselected group of cases with diabetes mellitus, duodenal tubes, placed with the aid of a fluoroscope and feeding cream by mouth, depressed the pancreatic enzyme (lipase, protein) output in 49% of the cases and had no effect on the remaining subjects. The investigator concluded that the diabetes mellitus altered the external secretory activity of the pancreas. This conclusion is open to question since the stimulus was given orally and we have no way of identifying the nature of the material that actually entered the duodenum. In other studies on patients with diabetes mellitus (41–44), in which acid fat or magnesium sulfate was administered into the duodenum through a duodenal tube, it was noted that the pancreatic volume, trypsin and lipase were depressed or the amylase and trypsin concentrations were not altered. These investigators did not position the duodenal tubes fluoroscopically. Over the next decade, only a few pancreatic exocrine studies were carried out on diabetic patients (45–47). In one report in which basal pancreatic secretions from four diabetic patients were compared to the pancreatic secretions of a control group, one diabetic patient showed a depressed pancreatic amylase and another diabetic showed a reduced pancreatic bicarbonate (45). This reduction in pancreatic amylase and bicarbonate was also noted in 18 diabetic patients after injections of secretin (46). Pancreatic insufficiency was not observed in diabetic patients treated with insulin (47). This observation was verified by two groups of investigators (48, 49) who reported no alteration in pancreatic secretion to secretin-stimulation in insulin-treated diabetic patients compared to control subjects. However, in other reports with the secretin test (50, 52), the pancreatic volumes (50, 51), the bicarbonate (50–52) and the enzymes (51, 52) of insulin-treated diabetic patients were depressed. These data could not be correlated with the age of the diabetic patient nor with the length of time of the disease (51).

During the past two decades, more studies were carried out on diabetic patients but the data appear to raise more questions than are answered. First, in those studies in which duodenal tubes were placed fluoroscopically in diabetic and nondiabetic patients, the pancreatic secretory responses to secretin-pancreozymin were similar (53–55). Second, in another series in which duodenal tubes were positioned fluoroscopically in diabetic and nondiabetic subjects, the basal pancreatic response and the response to secretin and to secretin-pancreozymin were dissimilar (56–64). In diabetic patients, the basal pancreatic secretion of enzymes was depressed (61), the secretin-stimulation of pancreatic volume (60, 64) and pancreatic bicarbonate (59, 60, 64) were reduced, and the secretin-pancreozymin stimulation of pancreatic volume (59, 60, 63), pancreatic bicarbonate (57, 62, 63), and pancreatic enzymes (56–58, 62, 63) were depressed. Third, in a series of studies in which duodenal tubes were placed fluoroscopically in juvenile diabetics and juvenile control subjects, the basal pancreatic secretion and the pancreatic secretory responses to secretin-pancreozymin were dissimilar (56, 57, 61, 62, 65). In the diabetic-subjects, the basal pancreatic secretion of enzymes was depressed and the secretin-pancreozymin stimulation of pancreatic volume, pancreatic bicarbonate, and pancreatic enzymes were reduced.

Thus, two groups of investigators disagree on the role of diabetes mellitus on pancreatic exocrine secretion and the data from both groups appear correct. Since the collection techniques used by these investigators were essentially similar and cannot be faulted, then perhaps it was the state of the exocrine pancreas in diabetes mellitus that varied. Some investigators (59, 60) stated that no diabetic patients with pancreatitis were included in their study, while in another group (57) one sixth of the diabetic patients had pancreatitis. In a review of 10,000 patients with diabetes mellitus, 2.5% of the patients had acute or chronic pancreatitis. This variable is most difficult to control. Pre-existing diabetes cannot always be ruled out in patients presenting with acute pancreatitis. It has been stated that pancreatitis occurs twice as often in diabetics than in nondiabetic subjects (66). The mechanisms by which diabetes mellitus induces pancreatitis has not been determined, but it has been proposed that hyperlipemia (67), a diminished resistance to infection (68) and small vessel disease (66), all common in diabetes, might be among the responsible factors. In addition, it is proposed that neither the duration of the disease (57) nor the role of insulin (57, 62) play a part in regulating pancreatic exocrine secretion. However, one study (59) suggested that the age of the diabetic patients modified pancreatic exocrine secretion although studies of exocrine pancreatic function in nondiabetic subjects have suggested no deterioration as a function of age (67, 70). In other studies, it has been demonstrated that the duration of the disease (59, 62, 65, 71) and the role of insulin were important in the pancreatic exocrine secretion of diabetic patients (59, 62, 65, 71). In two reports, it was suggested that juvenile onset diabetic patients with less than ten years' history and good control have a better exocrine pancreatic secretory response to pancreatic stimulation than less well-controlled patients with diabetes of similar duration (61, 72). The reduction of both the pancreatic enzyme and pancreatic bicarbonate secretory capacity in insulin-dependent patients was observed to be equivalent to the exocrine pancreatic dysfunction in nondiabetic patients with chronic pancreatitis (73). It has also been reported that diabetic patients have a reduced capacity to secrete gastric juice (74–82). Basal (75, 83–85), histamine (74–76, 83, 85, 86), pentagastrin (80–83, 87), insulin-induced hypoglycemia (80, 82, 87), and sham feeding (79) stimulated gastric secretion was reduced, with 17% to 70% of the patients with diabetes mellitus exhibiting an achlorhydria (74–76, 86) In one study (79), the gastric secretory responses of patients with diabetes mellitus were compared to control subjects. In the diabetic patients, pentagastrin stimulated gastric secretion was not reduced while sham feeding stimulated gastric secretion was depressed. This appears to indicate that the reduced gastric secretion of diabetic patients was not the result of a reduced gastric secretory capacity. However, in a study (83) in which the gastric secretory responses of patients with diabetes mellitus were depressed to histamine and pentagastrin stimulation, marked atrophic changes were noted in the fundic gland area. It has also been shown that peptic ulcer disease seldom exists with diabetes mellitus (88–90). In one study (89), the researchers own statistical materials as well as reports from the literature demonstrated that both diabetes mellitus and peptic ulcer disease was present in only 51 cases (0.49%) out of a group of 10,397 patients with diabetes mellitus. We are now faced with a paradoxical situation. Less acid in the stomach is available to block the release of antral gastrin and food stays a longer period of time in contact with the gastric antral mucosa because diabetic patients have a slow gastric emptying rate (79, 91–94). This causes an augmented serum gastrin which should result in an increased pancreatic exocrine flow. The reduced gastric acid results in a decreased acid chyme in the duodenum and a depressed release of secretin and pancreozymin which should result in a reduced pancreatic exocrine flow. These divergent data could be reconciled if we accept the reports that the degree of morphologic damage to the acinar pancreas in diabetes mellitus alters pancreatic secretion and the reports that diabetes mellitus modifies the acid-secretin-pancreozymin mechanism and the release of gastrin.

Recently, patients without diabetes mellitus, patients with diabetes mellitus, and parenchymal pancreatic damage were compared by scintography using (75) Se-selenomethione (95). The pancreatic uptake of the isotope in nondiabetic patients reached a plateau of 400 cpm within 20–30 minutes and the radioactivity sharply decreased to an intravenous injection of secretin-pancreozymin. The pancreatic uptake of the isotope in diabetic patients with pancreatic disease reached a pleateau of 200 cpm with 20–30 minutes and the radioactivity did not respond to an injection of secretin-pancreozymin. The response of the diet-treated diabetic patients ranged between the two groups. In another study with a (75) Se-selenomethionine scan, insulin-dependent diabetics exhibited a pancreatic abnormality of 85.7% (96).

The Effect of Hyperglycemia on the Exocrine Pancreas

Hyperglycemia in Animals

In an in-vitro perfusion of rat pancreas with Krebs-Ringer solution, glucose reduced the amylase secretion by 30% over a two-hour period (97). However, in a study in which rats received a continous infusion of glucose, that left the blood glucose level above 200 mg% and the immunoreactive insulin raised to 130μU/ml, the amylase content of the pancreas was elevated 25%, the lipase and chymotrypsin content was reduced by 25% and the rate of total protein synthesis was elevated over 40% (16). The carbomycholine-stimulated discharge of newly synthesized proteins were not altered and electron microscope appearance of the pancreatic acinar cells appeared normal (16). In anesthetized rabbits, the intravenous infusion of glucose with the resultant hyperglycemia induced an augmented pancreatic volume (98–101) trypsin output (98), and lipase concentration (97–101). The intravenous infusion of 20% glucose into cats also resulted in an increased pancreatic volume and lipase concentration (99).

The role of hyperglycemia on the canine exocrine pancreas has been variable. In 1921, it was noted that the introduction of cane sugar and acid through a gastric fistula in a dog with a permanent pancreatic fistula, stimulated a flow of pancreatic juice rich in trypsin (99). Unfortunately, we know little of the composition of the solution or its possible site of action. In studies on unanesthetized dogs with permanent pancreatic fistulae, the intraduodenal infusion of 5% glucose reduced basal pancreatic flow (102) and secretin-stimulated pancreatic flow (103) but neither the pancreatic amylase nor lipase concentrations were altered (102). In an unusual series of experiments (104–108) the head of a dog was completely isolated from the trunk except for the vagus nerves. The heads of these dogs (recipients) were perfused with blood from second dogs (donors) by means of cross-circulation. A plateau of pancreatic secretion was established with secretin in the recipient dog trunk and an intravenous infusion of 20% glucose into the donor dogs making these dogs and the head of the recipient dogs hyperglycemic. It was claimed that the hyperglycemia in the head of the recipients stimulated the vagus with a resultant augmentation of the pancreatic volume, lipase, trypsin and amylase. These observations could not be verified by another group of investigators (109, 110). Further, it had been reported that the intravenous infusion of 20% glucose into dogs increased their pancreatic volume and lipase concentration (99, 108), while in another study (111) the intravenous infusion of 20%–30% glucose depressed pancreatic volume and amylase concentration stimulated by secretin and cholecystokinin. There was a direct relationship between the concentration of glucose infused and the depression of pancreatic juice (111). In unanesthetized dogs with permanent pancreatic fistulae and gastric fistulae to divert gastric juice to the outside, the intravenous infusion of 2.5%–20% glucose, which caused a hyperglycemia, reduced pancreatic volume, protein, amylase and lipase concentrations (112) while in another study, pancreatic flow was not altered and pancreatic amylase concentration was increased (113). Finally, in unanesthetized dogs, the intravenous injection of glucose depressed the pancreatic volume and enzyme concentrations (114). The intravenous infusion of glucose into dogs increased the plasma insulin concentration in the superior pancreaticoduodenal vein (145). When insulin levels in anesthetized dogs were measured by bioassay, the rate of insulin secretion was found to be a continuous function of the blood sugar level, falling in pholaridzin-induced hypoglycemia and rising in glucose-induced hyperglycemia (116). These variations in the results might be caused, in part, by the following factors:

A. Blood Flow: Hyperglycemia induced by the intravenous infusion of 5% glucose augmented porcine pancreatic blood flow as measured by the hydrogen gas clearance (117). The rate of the increased pancreatic blood flow might have varied with different rates and concentrations of glucose infusion.

B. Serotonin: Hyperglycemia, induced by the intraduodenal infusion of 50% glucose, depressed pancreatic exocrine secretion and caused vomiting, defecation and restlessness (102). It was postulated that this inhibition of pancreatic secretion was caused by the release of serotonin. However, in another study, the intraduodenal infusion of small amounts of 50% glucose could reduce pancreatic exocrine secretion without the attendent subjective symptoms (103). It was postulated that serotonin was not necessary to inhibit pancreatic secretion. Varying concentrations of hypertonic glucose that were infused at different rates (102) could have been responsible for the added release of serotonin at the same time pancreatic secretion was being inhibited by the hypertonic glucose.

C. Antidiuretic Hormone: It has been demonstrated that antidiuretic hormone (ADH) can inhibit pancreatic exocrine secretion (118) and the intravenous infusion of hypertonic solutions has been shown to release ADH (118). The concentration and rate of glucose infusion can modify the release of ADH which in turn can depress pancreatic exocrine volume and this might have been responsible for some of the reported inhibition of pancreatic exocrine secretion. However, ADH does not reduce pancreatic enzyme activity.

D. Gastric Effect: The intravenous infusion of glucose into chronic gastric fistulae dogs depressed gastric secretion induced by sham-feeding (119, 120). The hyperglycemia could either reduce pancreatic exocrine activity by depressing the acid-secretin-pancreozymin effect in the duodenum or augment pancreatic exocrine secretion by the increased release of gastrin.

E. Species Differences: This might explain the augmented pancreatic responses in rat, rabbit, and cat and the depressed pancreatic responses in the dog to induced hyperglycemia.

Hyperglycemia in Man

Approximately 50 years ago, it was reported (121–124) that the infusion of dextrose into the small bowel of patients caused an initial increase in the flow of pancreatic juice (121–123) and, after a short period of time, the hyperglycemia which resulted, caused either a depression of pancreatic exocrine secretion (121–123) or an augmentation in the pancreatic enzymes amylase, lipase and trypsin (124). In the subjects, in which duodenal tubes were placed fluoroscopically and a continuous intravenous infusion of secretin-pancreozymin was maintained, an infusion of glucose into the small bowel which did not cause any subjective symptoms, reduced the pancreatic volume and bicarbonate but had no effect on the protein concentration (125). This infusion of glucose into the small bowel also increased the plasma levels of immunoreactive glucagon and insulin (125). However, in another study, the infusion of 2.5%–20% glucose into the duodenum had no effect on pancreatic volume, bicarbonate or protein concentration (126).

It was also noted approximately 50 years ago that the intravenous infusion of dextrose decreased pancreatic exocrine secretion in man without any initial increase in the pancreatic exocrine flow (121–123) while in one study the induced hyperglycemia augmented pancreatic volume and lipase outputs (127). When the induced hyperglycemia was imposed upon a test meal, pancreatic trypsin was suppressed (128), but when the intravenous infusion of glucose did not raise the blood glucose levels out of the normal range, no effect was noted on the pancreatic exocrine volume, bicarbonate or enzymes stimulated by the intravenous infusion of secretin (129). Finally, in two studies on patients with external pancreatic fistulae, the intravenous infusion of glucose had no effect on pancreatic secretion (130) while in the other study in which the blood glucose level was raised to 750 mg% there was a sharp decrease in the pancreatic volume and amylase (131).

Hyperglycemia can also indirectly influence the human pancreatic exocrine response for it can suppress food-stimulated gastric secretion 128, 132) and the level of circulating gastrin (128). Hyperglycemia can therefore reduce pancreatic exocrine activity by depressing the acid-secretin-pancreozymin effect in the duodenum and by suppressing the level of circulating gastrin which acts directly on the pancreas. The mechanism whereby changes in blood glucose levels influence gastric secretion is thought to be a vagally mediated effect on glucose-sensitive receptors in the hypothalamus (133). Whether the results can be extrapolated to diabetic subjects with chronic hyperglycemia, remain speculative for there appear to be differences in hormonal responses following intravenous and oral glucose. Finally, the gastric inhibitory polypeptide that depresses gastric acid secretion (134) is also released by oral glucose (135) and its insulinotrophic effect is probably important in the regulation of blood glucose after eating.

The Effect of Hyperinsulinism on the Exocrine Pancreas

Hyperinsulinism in Animals

No data could be located.

Hyperinsulinism in Man

Hyperinsulinism, caused by islet cell tumors, results in some diarrhea (136), atrophy of the pancreas (137), some slight increased fat in the pancreatic interlobular connective tissue spaces (137, 138) and a considerable increase in pancreatic connective tissue (137). A light and electron microscopic study of the exocrine pancreas of six patients with insulinomas revealed an exceptionally high number of centroacinar and ductal cells or a ductal epithelial hyperplasia (139). No pancreatic exocrine studies on patients with hyperinsulinism could be identified.

The Effect of Hypoglycemia on the Exocrine Pancreas

Hypoglycemia in Animals

Insulin had no effect on the amylase or chymotrypsinogen activity in organ cultures of chick embryo pancreas (140). In studies in which microdissected pieces of mouse exocrine pancreas were incubated (141, 142), the addition of insulin stimulated the oxidation of D-glucose but not that of amino acids. Insulin had no effect on the transport of amino acids into the exocrine cells but reduced the amylase secretion. In homogenized mouse pancreas, chymotrypsinogen activity gradually decreased from birth, reaching the adult level on day 20. Insulin had no effect on this chymotrypsin activity (143). In another study on homogenized mouse pancreas, amylase activity gradually increased during the last stage of gestation, decreased after birth and then gradually increased reaching the adult level on day 35. The addition of insulin to the homogenate retarded the pancreatic amylase during the postnatal development (144).

In rat studies, the pancreatic duct was cannulated and the pancreas was isolated and perfused with a Krebs-Henseleit solution. Pancreozymin augmented the output of amylase and insulin-induced hypoglycemia did not further increase this amylase output (145). In another study in which the rat uncinate pancreas was incubated in a Krebs-Ringer solution with bicarbonate buffer, glucose and albumin, pancreozymin and acetylcholine accelerated the release of both (45) calcium and amylase in a dose-dependent fashion while insulin (0.1 μ/ml) did not influence calcium release (146). However, no mention was made of hypoglycemia. In the rat pancreas, insulin appears to regulate amylase synthesis at the level of transcription, for the amylase messenger ribonucleic acid can only be synthesized in the presence of insulin (13). In a study in which insulin reduced rat blood glucose levels over a three-hour period, the pancreatic amylase concentration was increased during the first hour and reduced over the subsequent two hours (147). Studies on rats with chronic fistulae of the pancreas, in which acid was dripped into the duodenum to release secretin, insulin-induced hypoglycemia augmented pancreatic volume, total protein output and amylase concentration (148). In another study on rats with chronic pancreatic fistulae, insulin-induced hypoglycemia which increased pancreatic volume and amylase concentration, could be abolished by vagotomy (149). In both chronic rat studies, the insulin-induced hypoglycemia probably acted by augmenting vagal activity which increased the amount of gastric juice entering the duodenum and by stimulating the secretin-pancreozymin mechanism, and by increasing the release of gastrin. Finally, when the circulating levels of insulin in the rat were raised by the application of glibenclamide, pancreatic protein synthesis was raised 26% and the baseline discharge of amylase was increased by 50% (16).

In acute studies on anesthetized rabbits, electrical stimulation of the vagus resulted in an augmented pancreatic flow and lipase concentration which could be reduced by insulin (101). This insulin-induced inhibition was not caused by exhaustion of the exocrine pancreas since the injection of pilocarpine or acetylcholine increased the output of enzymes from the gland (101). In the rabbit, insulin-induced hypoglycemia reduced pancreatic volume, pancreatic trypsin and pancreatic lipase and this inhibitory response could be eliminated by vagotomy (98, 99, 101).

In a study in which pancreatic juice was collected from the isolated feline pancreas preparation, the intravenous infusion of secretin augmented pancreatic flow and cholecystokinin increased amylase output, but insulin had no effect on the exocrine pancreas (150). In an acute experiment on anesthetized cats, insulin-induced hypoglycemia reduced pancreatic volume and trypsin concentration (99). The inhibitory effect in the rabbit and cat might be due to a species difference. When anesthetized pigs were studied, insulin reduced pancreatic blood flow though the blood sugar levels were sustained by the continuous infusion of glucose (117).

In canine studies in which the pancreatic duct was cannulated and the pancreas was isolated and perfused with a Krebs-Henseleit solution, pancreozymin augmented the output of amylase and insulin-induced hypoglycemia did not further increase this effect (145). Insulin produced its influences only when its concentration was in large excess over the normal plasma levels. In acute canine experiments in which the stomach was surgically separated from the duodenum and the main pancreatic duct was cannulated, an augmented pancreatic secretion was reported following intravenous insulin (151). Unfortunately, no blood sugar determinations were made. In other acute studies on anesthetized dogs with their main pancreatic duct cannulated, insulin-induced hypoglycemia reduced the pancreatic volume pancreatic trypsin, pancreatic lipase and pancreatic amylase (99, 152–154). This reduced pancreatic secretion to insulin-induced hypoglycemia was also induced in hepatectomized dogs (154–155). In a series of acute studies, the head in one dog was completely severed from the body except for the intact vagal nerves. This head (recipient) was perfused with blood from a second dog (donor) by means of cross-circulation. Insulin-induced hypoglycemia in the donor dog augmented pancreatic volume in the recipient dog (104, 105, 153). The effect was thought to act over the vagal nerves. However, these experiments could not be repeated by another investigator (110). In other acute canine studies, insulin-induced hypoglycemia had no effect on pancreatic secretion (156–159). Finally, in acute canine studies, insulin-induced hypoglycemia produced a small but definite increase in pancreatic exocrine secretion (160). More recently, when chronic canine gastric fistulae were left open to drain gastric acid to the outside, insulin-induced hypoglycemia caused a slight increase in pancreatic bicarbonate and protein output from chronic pancreatic fistulae (161–163). However, when the gastric cannulae remained closed, so that the gastric juice drained into the duodenum to stimulate secretin-pancreozymin, a marked increase occurred in the pancreatic bicarbonate and protein (163). When insulin-induced hypoglycemia was imposed on a continuous infusion of secretin in unanesthetized dogs with chronic pancreatic fistulae and gastric juice was prevented from reaching the duodenum, the pancreatic trypsin was augmented but there was no effect on the pancreatic volume (164). In other studies on unanesthetized dogs with chronic pancreatic fistulae, the increased pancreatic exocrine volume induced by insulin-induced hypoglycemia could be abolished by bilateral vagotomy or by the exclusion of gastric juice from the duodenum (114). No direct relationship was observed between canine pancreatic blood flow and pancreatic venous insulin concentration (165). In dogs, it appears that the augmented pancreatic exocrine response to insulin-induced hypoglycemia acts though the acid-secretin-pancreozymin mechanism.

Hypoglycemia in Man

Forty to fifty years ago, it was reported that insulin-induced hypoglycemia acted centrally (166–169) to increase human pancreatic exocrine secretion (166–169). When insulin hypoglycemia was induced in subjects whose gastric juices were excluded by the continuous aspiration of the stomach or in individuals with gastric achylia, the pancreatic volume (170–174) and enzymes (124, 170–174) were increased while the bicarbonate was not altered. In other older studies, insulin-induced hypoglycemia did not alter pancreatic volume, protein, lipase and amylase in patients with pancreatic fistulae (175, 176). In more recent studies on subjects with duodenal aspiration, insulin-induced hypoglycemia did not modify secretin-stimulated pancreatic volume (177, 178) or bicarbonate but augmented pancreatic enzymes. (170, 172, 177–179). However, in studies on patients with posttraumatic pancreatic fistulae, insulin induced hypoglycemia augmented pancreatic volume and amylase (131, 180).

Data on the effects on insulin-induced hypoglycemia on the exocrine pancreas are complicated by the multiple actions of the insulin. The hypoglycemia which has a stimulatory action on the vagus nerves may cause a) the release of gastrin which stimulates the secretory activity of the exocrine pancreas b) an augmentation of gastric juice which enters the duodenum and causes the release of secretin and pancreozymin which stimulates the secretory activity of the exocrine pancreas and c) the direct release of secretin and pancreozymin which stimulates the secretory activity of the exocrine pancreas. In addition, investigation of the effects of hypoglycemia on the external secretion of the pancreas poses special problems such as the uncertainty of quantitative recovery of pure pancreatic juice and the difficulty of excluding gastric juice from the duodenum to prevent the secretin-pancreozymin mechanism. Therefore, an attempt was made to explain these actions by comparing the vagal actions of insulin-induced hypoglycemia with other types of vagal stimulation.

Electrical stimulation of the vagus nerves caused a reduction in feline antral gastrin activity (181), with an augmentation in cat (182–186) and dog (187–191) serum gastrin levels as measured by radioimmunoassay or an increase in feline (182–192) and canine (193, 194) gastrin secretion. The gastrin acted directly on the exocrine pancreas while the gastric juice operated through the secretin-pancreozymin mechanisms. Electrical vagal stimulation also increased the pancreatic volume in rabbit (195, 196), cat (197), dog (191, 198–203), and pig (202, 204–208) and augmented the pancreatic volume response to secretin in cat, dog, and pig. This augmented pancreatic exocrine response to electrical vagal stimulation was not altered by gastric antral resection in the pig (207). This electrical vagal stimulation increased the bicarbonate content of pancreatic juice in pig (202, 207, 208) and augmented the pancreatic bicarbonate response to secretin in cat and pig (208, 209). Finally, electrical vagal stimulation increased the flow of pancreatic enzymes in rabbit, cat, dog and pig and augmented the pancreatic enzyme response to secretin in cat (196, 197, 209–211) and pig (202, 206, 208). Therefore, electrical stimulation of the vagal fibers increased serum gastrin levels, pancreatic exocrine secretion and the sensitivity of the exocrine pancreas to secretin. In addition, electrical stimulation of the vagi in dogs (212) and baboons (213) resulted in elevated serum insulin levels as measured by radioimmunoassay. This insulin release to vagal stimulation was not secondary to hyperglycemia since the blood glucose levels were not altered (213). The effect of electrical vagal stimulation on the pancreatic exocrine secretion varied among species. In pigs, there was a larger water and protein output (207), while in cats and dogs the response was smaller. However, when electrical stimulation was applied using a secretin background, the canine pancreatic volume and protein secretion were sharply increased (191). Electrical vagal stimulation in the dog did not increase serum secretin nor serum pancreozymin levels. Since the physiologic release of both secretin (214) and pancreozymin (215) had previously been demonstrated, these results provide direct evidence that these hormones are unlikely to be under vagal control and that the effect of vagal stimulation on pancreatic secretion is probably not mediated by them.

In 1890 (198), it was demonstrated in Pavlov's laboratory that the gastric secretory response to sham feeding was mediated by the vagus nerves. Sham feeding augmented the flow of gastric juice in dog (216–221) and man (222, 223) and increased serum gastrin levels in dog as measured by secretion from Heidenhain pouches (221, 224–228) and by radioimmunoassay (219, 220) and in man as measured by radioimmunoassay (229). When sham feeding was superimposed on an intravenous infusion of gastrin, in antrectomized dog with a Pavlov pouch, gastric secretion was augmented (230). Sham feeding stimulation increased the pancreatic volume in rat (231) and man (232) and augmented the pancreatic volume response to secretin in dog (233). This stimulation also increased the bicarbonate content of human pancreatic juice (232) and the flow of pancreatic enzymes in rat, dog, and man and augmented the pancreatic enzyme response to secretin in the dog. This pancreatic response to sham feeding was inhibited by acidification of the pyloric gland area (234) which suggested that part of the pancreatic response to sham feeding was mediated by the vagal release of gastrin from the pyloric antrum. In this study (234) the gastric fistula was kept open to prevent acid from entering the duodenum and activating the secretin-pancreozymin response suggesting that sham feeding stimulated the vagal release of gastrin from the pyloric gland area. Therefore, sham feeding increased serum gastrin levels, gastric secretion, and the acid-secretin-pancreozymin pancreatic effect and the sensitivity of the exocrine pancreas to secretin.

All investigators who used acceptable methods reported a marked increase in gastric secretion accompanying insulin-induced hypoglycemia provided the subject was able to secrete acid (235). This vagal stimulus increased gastric secretion in dog (217, 218, 236–241) and man (242–246) and augmented serum gastric levels in dog as measured by secretion from Heidenhain pouches (221, 226) and by radioimmunoassay (241, 247, 248) and in man as measured by radioimmunoassay (229, 245, 246, 249, 250). In man the augmented serum gastrin level to insulin-induced hypoglycemia was not abolished by vagotomy (251, 252). Vagal stimulation by insulin-induced hypoglycemia evoked canine gastric secretion after resection of the gastric antrum and the removal of known gastrin sources (253).

The following conclusions might be drawn from these data. One, all three stimuli increase the gastric acid output and the passage of acid into the duodenum released secretin and pancreozymin with an augmented pancreatic response. Two, all three stimuli increased the release of gastrin which acted directly on the exocrine pancreas to augment pancreatic secretion. Three, sham feeding and electrical stimulation of the vagi have a direct effect on the exocrine pancreas to release pancreatic volume, bicarbonate, and enzymes. Four, sham feeding, electrical stimulation of the vagi and insulin-induced hypoglycemia increased the sensitivity of the exocrine pancreas to secretin stimulation. Finally, electrical stimulation of the vagi did not increase serum secretin nor serum pancreozymin levels. Therefore, the insulin-induced hypoglycemic effect in rats, dogs and man augmented pancreatic exocrine secretion by a multiple of actions.

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The Treatment of Glaucoma Secondary to Aniridia

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Abstract

Aniridia is a congenital anomaly in which all but the peripheral iris is absent. The disease is usually inherited through an autosomal dominant gene with high penetrance and variable expression. Numerous ocular and systemic abnormalities may be associated. There is a high incidence of associated Wilms' tumor. Most cytogenetic studies indicate an interstitial deletion of the short arm of chromosome 11 to be the most consistently found defect. Secondary glaucoma occurs usually in the second to third decade due to gradual apposition of the iris stump to the trabecular meshwork. This results in an unusually severe glaucoma. Medical treatment is inadequate and the results of surgery are frequently poor. Prophylactic goniotomy may be a means of preventing later onset of glaucoma.

Aniridia is a congenital anomaly in which all but the most peripheral part of the iris is absent at birth. It was first described by Barratta (1) in 1819 and the first pedigree published by Gutbier (2) in 1837. The term "aniridia" is used in the clinical sense only, as a short iris stump is hidden behind the corneoscleral limbus and can frequently be visualized only with a gonioscopic prism. It is a relatively rare entity, the incidence being estimated at 1/100,000 in Denmark (3) and at 1/56,000 in Michigan. (4) There is an equal sex distribution, and bilateral cases are 50 times as common as unilateral cases.

Although aniridia can appear in the absence of a family history (sporadic due to a new chromosomal mutation), approximately two-thirds to three-quarters of cases are inherited in an autosomal dominant fashion with high penetrance and variable expression. Infrequent autosomal recessive cases between consanguineous patients have been described. Autosomal dominant aniridia is frequently associated with other ocular abnormalities, such as microphthalmos, strabismus, nystagmus, spherophakia, cataract (Fig. 1), ectopia lentis, and corneal dystrophy. It is invariably associated with some degree of macular hypoplasia with resultant decrease in visual acuity. Treatment is directed toward individual symptoms. Cataracts frequently require lens extraction by early adult life. Nystagmus and photophobia may be treated with contact lenses, and decreased visual acuity, caused by macular hypoplasia, with visual aids. In addition to ocular abnormalities, familial aniridia may be associated with multiple systemic congenital defects, including polydactyly, aberrant spleen, dysostosis of the skull and face, malformations of the extremities, hydrocephalus, and mental retardation (5).

Glaucoma, which usually develops in early adult life, occurs in 50% to 75% of cases (6). The severity of the glaucoma correlates well with the extent of gonioscopically visible obstruction of the filtration portion of the trabecular meshwork by the iris stump (Fig. 2). When untreated, it is this secondary glaucoma that robs the aniridic of the limited sight that he was born with.

The Embryology of Aniridia

The iris is formed by forward growth of the rim of the neuroectodermal optic cup into a loose stroma of mesenchymal tissue. In the normal iris,

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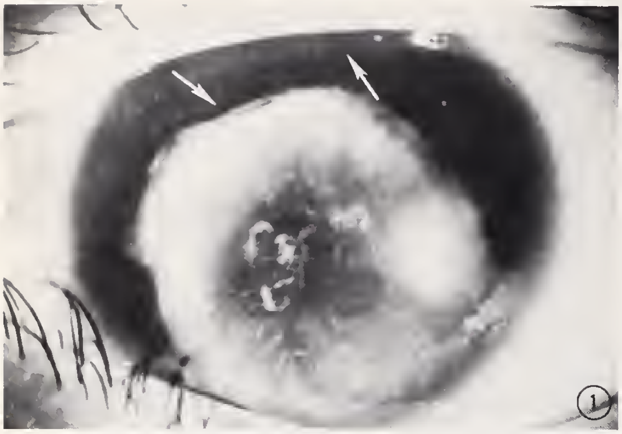

FIG. 1. Aniridic right eye of a 16-year-old girl with sporadic aniridia. White arrows point to the margins of the iris stump. A dense congenital cataract is present centrally.

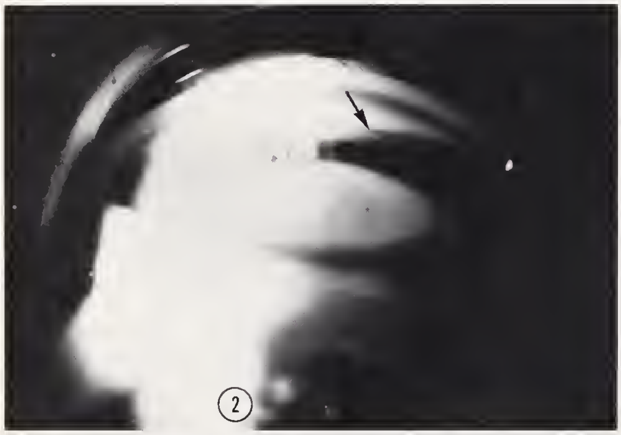

FIG. 2. Gonioscopic view of the angle of the same patient. The ciliary processes are easily seen between the iris stump and the lens on gonioscopy and are illuminated by the slit beam. The arrowhead points to the iris stump visible in the shadow of the beam which covers the entire trabecular meshwork.

the posterior pigment epithelium, sphincter, and dilator muscle are of neuroectodermal origin, while the richly vascularized connective tissue stroma is mesodermal. The iris stump of the aniridic contains both mesodermal and ectodermal elements in a highly underdeveloped form. Pedigrees have shown various relative combinations of stromal and pigmented tissue in the iris stump even among siblings. Although a theory involving primary mesodermal failure (which would inhibit normal forward growth of the optic cup) has been proposed, the commonly accepted theory has been that of primary ectodermal failure (7).

The ectodermal failure theory proposes that a germinal arrest of the differentiation of neuroectodermal cup rim occurs in the 70–80 mm embryo. At this time, the mesodermal iris is present and formed, the ectodermal iris exists as a narrow rim just beneath the corneoscleral margin, the retinal layers have been differentiated, and the area centralis has been mapped out but has not differentiated into the fovea. When the rim of the cup does not grow forward, the mesodermal stroma atrophies. This theory accounts for the presence of iris stump containing both embryologic tissue types, as well as the macular hypoplasia.

Although the lens arises not from neuroectoderm but from surface ectoderm that invaginates and develops into the lens vesicle, the rim of the cup is believed to exert some regulation on lens development. Without the growth of the rim of the cup, it is postulated that there is a decreased stimulus to the growth of the lens vesicle, resulting in associated lens anomalies, such as microphakia, lens opacity, and octopia lentis (as the zonular ligments of the lens arise from the primordial rim).

Elsas et al (8) investigated a family with 88 aniridics in six generations whose pedigree exhibited the classic autosomal dominant pattern. The incidence of associated ocular disorders, such as poor visual acuity (5%), cataracts (18%), and glaucoma (13%) was considerably lower than in other pedigrees reported. Elsas postulated that the primary defect was not ectodermal (which accounts for the foveal hypoplasia, cataracts, glaucoma) but mesodermal; therefore, primary mesodermal failure may be the etiology in some cases.

Sporadic Aniridia and Wilms' Tumor

In 1964, Miller et al (9) described the syndrome of Wilms' tumor, genitourinary abnormalities, and sporadic aniridia. An epidemiologic study of 440 cases of Wilms' tumor revealed an incidence of aniridia of 1:73 cases (approximately 1,000 times the incidence in the general population). All of the aniridia were of the sporadic type. These children displayed numerous other congenital defects, such as hemihypertrophy, microcephaly, mental retardation, abnormalities of the external ears, and urogenital abnormalities. The male:female ratio was 9:2. The frequency of Wilms' tumor patients with aniridia was estimated at 1:59 after the inclusion of five new cases by 1966. Fraumeni and Glass (10) estimated that about 33% of patients with severe sporadic anirida developed Wilms' tumor within the first year of life. This was confirmed by Pilling (11), who surveyed 26 infants and children with aniridia. Six were familial and did not develop tumor, while seven of the twenty with sporadic aniridia developed unilateral tumor. Average age at diagnosis was 22 months, which is close to Fraumeni's estimate of 1.8 years. Wilms' tumor not associated with the aniridia syndrome is usually diagnosed between three and six years of age, with an average age of 3.6 years.

Genetics

Although no formal agreement exists as to the classification of aniridia, the literature tends to group aniridics by their mode of inheritance. In Shaw's Michigan study, 4, 118 cases were assembled from a population of 7.6 million. Statistically estimating 18 undiscovered cases, he postulated an incidence of 1/56,000. Of these 118, approximately 1/3 were sporadic. No consanguinity between the parents of the sporadics was discovered. Patients were found to pass the disease to their offspring in a classic autosomal dominant fashion. A mutation rate of 4×10^{-6} mutations/locus/generation was calculated.

Neither the sporadic nor the familial cases deviated significantly from the expected 1:1 sex ratio, and all were noted to be visually handicapped. No cases of recessive transmission were identified, and there were no cases of the gene skipping a generation. The most striking finding was that the 38:62 ratio of affected to normal children in segregation sibships significantly deviated from the expected 50:50. Shaw attributed this to a "reduced fitness of the aniridia gene" and not a function of decrease penetrance, sibship size, sex of parent, infant mortality, or heterogeneity among kindred. The first literature report of a chromosomal defect in a patient with sporadic aniridia with unilateral Wilms' tumor at 19 months revealed a chromosomal translocation t(8p+, 11q−) with an interstitial deletion of the short arm of eight (12). Hittner, Riccardi, and Francke reported a child with sporadic aniridia, multiple anomalies, severe failure to thrive, and psychomotor retardation (13). No Wilms' tumor was present in the girl by ten months of age. Cytogenetic studies revealed an interstitial deletion of the short arm of chromosome 11 (46,XX,del [11p] [pter → p14::p11.3 → qter]). Six other recent cases of sporadic aniridia with mental retardation have been reported also to have a deletion of 11p. The deleted segment was termed the "Aniridia-Wilms' Tumor Haplicon." By converting the previously normal double dose of genetic material into a single dose by deletion, the triad of AGR (aniridia, genitourinary anomalies and retardation) results. It appears also that the association of sporadic aniridia and Wilms' tumor (AWTA) resides, at least in part, in this deletion. The size of the deletion may well be the determining factor with regard to associated manifestations.

The patient first reported (12) was restudied utilizing high-resolution trypsin-Giemsa banding of prometaphase chromosomes (14). A complex rearrangement was found involving breaks in 8p, 11p, and 11q with a net loss of the interstitial segment of the short arm of chromosome 11.

Aniridia, cataract, and gonadoblastoma were reported in a 21-month-old mentally retarded girl (15). Autopsy revealed tiny gonadal streaks with bilateral benign gonadoblastoma. No ovaries, Wilms' tumor, or other embryonal structures were detected. (Both Wilms' tumor and gonadoblastoma are embryonal mesodermal tumors believed to arise from mesonephric structures.) Chromosomal studies revealed an interstitial deletion of 11p.

A family with autosomal dominant aniridia with highly variable iris abnormalities, preserved ocular function, and the variable presence of associated ocular abnormalities was recently reported. Approximately 50% of the family members at risk had some iris abnormality. The authors suggested that incomplete slit-lamp examination of all family members who were at risk accounted for lower figures in previous studies. Of 16 affected cases in the study, six had complete or near-complete aniridia, colobomas (both typical and atypical) occurred in four, while minimal iris thinning with round pupils was found in the remainder. Apparently, many of the affected members were unaware of any ocular abnormalities, having round pupils and vision of 20/40 or better in at least one eye. No extraocular, genitourinary, or dental anomalies or mental retardation were present in any family member.

A computerized maximum likelihood analysis for linkage between autosomal dominant aniridia (ADAN) and 12 biochemical and serologic markers showed a probable linkage with the enzyme acid phosphatase-1 (17). This would place at least one gene responsible for ADAN on chromosome 2p. No mutations were detectable by prophase chromosomal analysis. The association of an ADAN gene with chromosome 2 and AWTA with 11p suggests that two independent genetic mechanisms which result in two different aniridia syndromes are operative.

A single family of autosomal dominant aniridics with glaucoma has been reported to have a pericentric inversion of chromosome 9 in all affected family members (18). Chromosome 9 is known to have high susceptibility for structural arrangements, such as inversions due to its large amount of satellite DNA with repetitive structures present in the heterochromatic area. At this time this finding may only be considered of interest, as no clear linkage of chromosome 9 and aniridia has been shown.

Mechanism of Glaucoma

Increased intraocular pressure is not present at birth, and corneal edema, photophobia, and buphthalmos are rarely seen (19). Glaucoma occasionally occurs in infancy with some corneal enlargement, but corneal enlargement tends to be much less than in infantile glaucoma (20). More commonly, glaucoma occurs in the preadolescent period and in early adulthood, and tends to progress in severity.

Although glaucomatous loss of vision may not occur until early adult years, progressive changes in the angle causing future glaucoma occur during childhood. Grant and Walton (21) followed sequential changes of the iris stump over several years in 31 aniridics. They confirmed that both the presence of glaucoma and its severity corresponded to the extent of gonioscopically visible obstruction of trabecular meshwork by overlying iris stump. Aniridic infants who eventually developed glaucoma had irregular fine attachments of iris stroma extending across the ciliary face and scleral spur in a sawtooth pattern and attaching to the trabecular meshwork. These were not seen in the eyes of those who remained normotensive. These attachments become denser with time, migrate forward, and pull the iris stroma against the trabecular meshwork, blocking off the outflow channels and resulting in elevated intraocular pressure. Gonioscopy of normotensive eyes reveals very little covering of the filtration portion of meshwork around most of its circumference, and the scleral spur can be seen for 360°. Mild cases of glaucoma have progressed to circumferential involvement by multiple stromal sawtooth projections. There may be some separation of iris stroma from posterior pigment epithelium as it begins to be pulled up toward the ciliary body band. In the more severe cases, the forward attachment of stroma covers at least the posterior one-half of trabecular meshwork in any meridian. The iris pigment epithelium may be left behind and vessels are not evident at this stage.

Medical Therapy of Glaucoma

The treatment of glaucoma has been primarily medical, surgical procedures being used only when medical treatment has proven inadequate. There is no surgical procedure of choice, and numerous approaches have been attempted with only moderate success at best.

Unlike other congenital glaucomas, medical treatment with miotic drops is often efficacious (22). Topical cholinergics and anticholinesterases commonly lead to at least a temporary improvement in intraocular pressures, by their effect on the ciliary muscle, (since there is no pupillary sphincter present in the rudimentary iris tissue). Increased outflow of aqueous occurs in unoccluded portions of trabecular meshwork. Epinephrine, timolol, and carbonic anhydrase inhibitors may also be of value.

Unfortunately, medical therapy does not control the progressive occlusion of filtration meshwork by iris stump, and eventually patients become refractory to medical therapy. Surgical treatment then becomes imperative to prevent total blindness.

Surgical Therapy of Glaucoma

In 1953, Blake (19) presented information solicited from many ophthalmologists. Of the 87 respondents, 41 claimed to have operated on at least one case. Less than 80 cases have been performed using several techniques, with failure to control pressures in almost 50% of the cases. No one surgeon had used any procedure a sufficient number of times to have a convincing opinion as to the best method. Procedures most preferred were cyclodiathermy, cyclodialysis, and goniotomy.

More than 25 years later, there is still no procedure of choice that can be considered predictably effective in a satisfactory percentage of patients. Despite Barkan's first success with goniotomy for aniridic glaucoma in a four and one half-month-old boy with bilateral aniridia (23), no real cures were obtained in Walton's 14 cases. Goniotomy involves the dissection of anterior stromal adhesions of the stump off the meshwork in order to expose scleral spur and ciliary body band. This procedure did allow some temporary improvement to miotic therapy by allowing increased exposure of the meshwork. When this operation is performed on glaucomatous eyes with previously damaged filtration apparatus, poor results are obtained. Despite this, Shaffer and Weiss still consider goniotomy as the initial procedure of choice (22).

If two or three separate goniotomies are unsuccessful, then filtering procedures, cyclodiathermy, or cyclocryotherapy can be considered. There is a significantly increased possibility of vitreous loss when filtering procedures are performed in an aniridic. Since the iris is not present to prevent inadvertent damage to the lens, cataract formation or progression may occur postoperatively.

In Walton's series (6), conventional glaucoma surgery, such as trephining, cyclodialysis, cyclodiathermy, and trabeculectomy were performed with no success on ten eyes. Only cyclocryotherapy was proven to achieve some measure of success in five eyes, but at the cost of an accelerated opacification of the peripheral corneal epithelium and cataracts in three. Transient postoperative vitreous hemorrhage occurred in one, and prolonged hypotony following cataract extraction occurred in another.

Grant and Walton are presently investigating prophylactic goniotomy in young infants. Patients with extensive early bridging of sawtooth iris synechiae on gonioscopy are candidates and are selected after being followed gonioscopically to evaluate the progression of changes in the angle. Surgery is not performed until after the first year of life due to the early shallowness of the anterior chamber. Two separate operations are performed on each eye to attempt to free more than one-half of the circumference of the angle. Removal of these attachments early in the progression of the disease will hopefully prevent physiologic changes that hinder future therapy. Glaucoma has not yet developed in any of the eyes, but a longer follow-up will be necessary to determine the value of the procedure. No postoperative complications, other than transient surgical hyphemas, have occurred.

The use of the laser in such surgery should be investigated. It is feasible to consider that the early attachments of iris stump to the trabecular meshwork may be prophylactically dissected, using the laser and thus avoiding intraocular surgery.

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Anesthesia for Major Noncardiac Surgery in a Patient with a Transplanted Heart

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Abstract

As the number of patients undergoing cardiac transplantation increases, and as the survival figures improve, there is a growing possibility that the anesthetist may handle such a patient for other surgery unrelated to the heart. We describe our experiences with a patient, four years postcardiac transplantation, who underwent two neurosurgical procedures. The preoperative assessment and anesthetic management are discussed.

Since December 1967, when Barnard performed the first successful human cardiac transplant, several hundred patients have undergone this operation (1). For those who survive the critical three months following transplantation, the three-year survival is recently reported as approaching 50%, and, consequently, more anesthesiologists will be dealing with such patients needing surgery either related or unrelated to cardiac problems (2). We present our experiences with a 48-year-old male with a transplanted heart, who received anesthesia without complications twice within three days for operations to decompress the cauda equina. This case report illustrates that anesthetic management of such patients is straightforward, provided their circulatory physiology is fully assessed at the outset.

Case Report

The patient, a 48-year-old male, was admitted to the Mount Sinai Hospital in November 1979, complaining of low back pain and wasting of his left lower limb. In the past, he had had a cardiomyopathy that had progressed to intractable heart failure. He had undergone cardiac transplantation in 1975 at Stanford University Hospital. Following transplantation, he made an excellent recovery, and, over the next four years, earned his living by traveling around the country as a professional (ten pin) bowler.

His neurologic symptoms had been interfering with his work for about six months. Three weeks prior to coming to The Mount Sinai Hospital, he fell while bowling. This aggravated the pain in his lower back and left leg which led to hospitalization and subsequent transfer to Mount Sinai Hospital. Neurologic examination at this time revealed atrophy, weakness, and hypotonicity in left quadriceps, hamstrings and anterior tibial muscle groups. There was also some atrophy and weakness of the right leg. The left knee jerk was absent, and sensation to pinprick was reduced in the L_3 to L_5 dermatomes. Because of excruciating low back and left leg pain, he could not walk unsupported, and spent most of his time lying supine with his left leg flexed on a pillow. Any movement brought on spasm of his back and left leg.

He denied exertional dyspnea, orthopnea, or angina. There were no symptoms of raised intracranial pressure. Since his transplant surgery, he had developed hypertension and glaucoma. His drug regime consisted of: prednisone 25 mg/day, azathioprine 200 mg qid, methyldopa 500 mg bid, furosemide 40 mg qid, aspirin, dipyrimadole, Titralac (calcium carbonate and glycine mixture), diazepam, and epinephrine 2% eyedrops.

He weighed 200 lbs and was 6′2½″ tall; blood pressure 140/110 torr, heart rate 74/min, regular. Cardiovascular system examination was other-

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wise normal. There was no evidence of decompensation and his chest was clear.

ECG showed regular sinus rhythm, with incomplete right bundle branch block suggestive of right ventricular hypertrophy. Chest x-ray was within normal limits. Serum electrolytes and liver function test results were normal; Hb 15.1 and Hct 45. Echocardiogram was normal.

The patient's most recent cardiac catheterisation and angiography had been in June 1979 at Stanford. Left ventricular end diastolic pressure (LVEDP) was 12 torr at rest and 13 torr following angiography (that is, following a fluid load). The coronary angiogram showed stenoses in the left anterior descending and left circumflex arteries. The ejection fraction was 53%, and the apical segment of the left ventricle was moderately hypokinetic.

Neurologic investigation at Mount Sinai included a lumbar myelogram that demonstrated an extradural mass extending from L_2 to L_4, but most prominently at L_3 level on the left side (Fig. 1). There was no evidence of bony changes. A radiologic bone survey revealed no metastases and no destructive lesion was seen on the radiographs of the lumbar spine.

The patient was scheduled for lumbar laminectomy and removal of the tumor. Dipyrimadole and aspirin were discontinued so that by the time of surgery the clotting mechanism was normal.

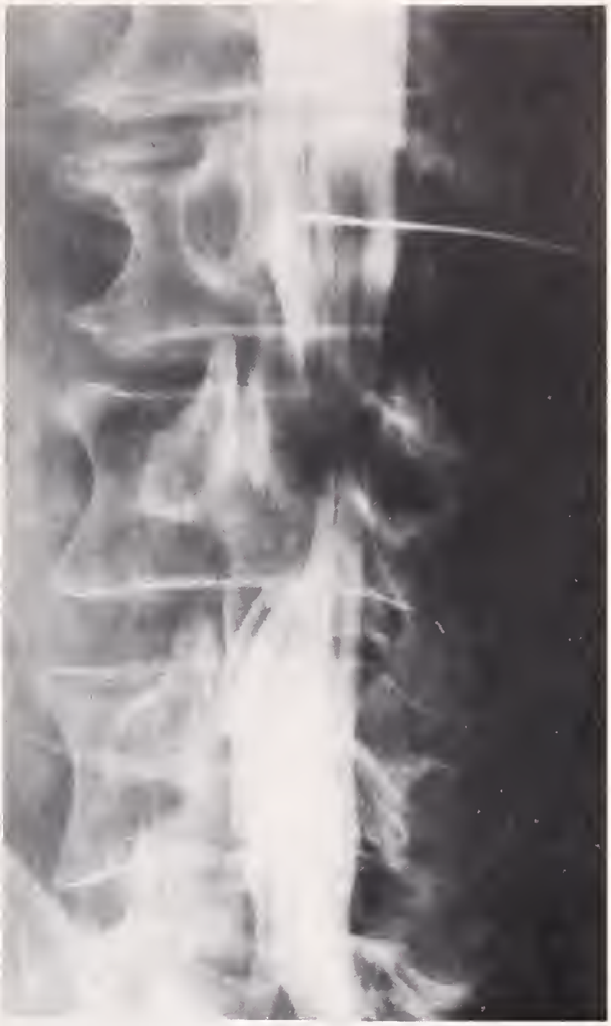

FIG. 1. Oblique view of lumbar myelogram using metrimazide. The cauda equina nerve roots are compressed by a large epidural mass which is maximum in size at L_3 level.

Anesthetic Management

For premedication, he received diazepam 20 mg orally, and was well sedated on arrival in the operating room. Since these patients are prone to opportunistic and nosocomial infections, invasive monitoring was avoided. It was proposed to monitor the blood solely by sphygmomanometer and to record the ECG (lead CM5) with surface electrodes (3). Using sterile precautions, an intravenous line was set up with a 14 gauge Angiocath in the right forearm. The following cardiovascular drugs were prepared and held available: propranolol 1 mg/ml, isoprenaline 1 mcg/ml, and dopamine 40 mcg/ml. Hydrocortisone 200 mg and diazepam 5 mg were given intravenously prior to induction. The patient was preoxygenated for five minutes and anesthesia was induced with a "sleep" dose of thiopental (200 mg) and fentanyl 100 mcg. Pancuronium 8 mg was given to provide relaxation and facilitate intubation.

Once relaxed, laryngoscopy was performed and the larynx was sprayed with 4 ml of 4% lidocaine. The patient was intubated smoothly with a 9.0 mm cuffed Portex endotracheal tube. During and immediately following intubation, the pulse rate remained steady at 74/min. and blood pressure remained stable at 130/100 torr. Controlled ventilation was started with 33% O_2 in N_2O using an Ohio ventilator, and the patient was placed in the right lateral oblique position for operation. Anesthesia was maintained with N_2O/O_2 (4L/2L) and supplements of curare 6 mg and fentanyl 50 mcg. Before the incision was made, vancomycin 1 gm IV and tobramycin 80 mg IM were given as intraoperative antibiotic prophylaxis, a routine in our neurosurgical operating room.

The anesthetic course was uneventful. When BP and HR rose slightly, increments of fentanyl or curare were given and these returned to normal after administration of these drugs. Temperature was maintained throughout at 36°C. No dysrhythmias were observed during the surgery, nor was there any variation of the pulse rate in phase with respiration.

Quarter strength saline in 5% Dextrose was used for replacement of fluid and blood losses. Care was taken to neither overload nor underhydrate the patient. He underwent lumbar laminectomy from L_2 to L_5 inclusive, and removal of a large epidural mass which was compatible with lymphomatous tumour. Total time under anesthesia was five hours. Blood was not required. Prior to reversal of relaxation, 1.2 mg atropine was given with no effect on the heart rate. After nitrous oxide was discontinued, the heart rate and blood pressure rose steadily. Neostigmine 3.0 mg reversed neuromuscular blockade, again, with no effect on the cardiovascular system.

During the return of spontaneous ventilation, the response to Valsalva was tested. There was no variation in heart rate or blood pressure.

The patient awakened in the operating room and was extubated and transferred to the cardiac intensive care unit for postoperative care. Recovery from anesthesia was uneventful, and after one day, he was returned to his room. Postoperatively, the ECG was normal.

On the second postoperative day, the patient experienced severe pain in his back and further weakness developed in his legs. Cauda equina compression caused by postoperative hematoma was suspected. He was returned to the operating room for re-exploration of the operation site. On arrival at the operating room, heart rate and blood pressure were elevated. Anesthesia was induced as before and both these values returned to normal. A large epidural hematoma was evacuated and the laminectomy was extended to include L_1. The anesthesia lasted four hours. After similar management technique, the patient made a good recovery from his anesthesia and surgery.

The patient was making a satisfactory postoperative recovery, with relief of preoperative leg pain and improving strength in both lower limbs. His only complaint was that of incisional pain. On the seventh postoperative day, as he attempted to get out of bed and walk, he suddenly developed cardiopulmonary arrest without any warning symptoms. Attempts at resuscitation were unsuccessful. A clinical diagnosis of deep vein thrombosis and massive pulmonary embolism was confirmed by autopsy.

Discussion

Patients such as the one described, present several problems in anesthetic management related to 1) cardiovascular hemodynamics, 2) abnormal immunologic state with low resistance to infection, and 3) complex drug therapy. If these issues are recognized and considered, the risks of anesthesia and surgery may be minimized.

First to be considered is the cardiac status. Transplantation is considered only in otherwise healthy patients with minimal noncardiac disease (4, 5). The operation is simple by cardiac surgery standards and involves periods on bypass of approximately one hour. The posterior atrial walls and entrant veins are retained and the aorta and pulmonary arteries are transected. The donor atria are then sutured to the recipient's atrial remnants. This technique reduces the number of anastomoses needed, and retains the innervation of the atria. The aorta and pulmonary vessels are then anastomosed.

Several cardiovascular problems result from this procedure. Since the transplanted heart is denervated, it cannot respond to neurally mediated stimuli (6). To date, there is no evidence in humans for reinnervation of the donor atrium (7). However, adrenergic receptors in the transplanted heart are intact so that it will respond to both endogenous and exogenous catecholamines. Consequently, the heart rate shows no response to atropine, digoxin, pancuronium or neostigmine administration, but will respond to isoprenaline, dopamine, or glucagon (8–10). The denervated heart responds to stress or exercise primarily by increasing stroke volume (11) (Starling mechanism) since changes in rate occur more slowly in response to circulatory catecholamines. In these patients, the stroke volume depends mainly on a) preload, and b) myocardial contractility and, to a much lesser extent, on c) afterload. The LVEDP is often greater than normal, thus ensuring adequate preload (6). Preoperative cardiac workup in our patient revealed an LVEDP of 12 torr (normal) at rest that increased to 13 torr postangiography (that is after a sudden fluid load) indicating a normal healthy myocardial response.

The resting heart rate was 74/min which is lower than that commonly found in transplanted patients (6, 12). It is possible that the donor heart had good inherent contractility requiring a lower level of circulatory catecholamines and resulting in a normal resting heart rate. During the surgery, there were gradual changes in rate and these are probably produced by circulating catecholamines. Thus, as the anesthesia became "lighter," the heart rate increased slowly. It decreased following the administration of fentanyl ("deepening" anesthesia).

The blood pressure remained stable throughout surgery despite the patient's hypertension and antihypertensive therapy (13). These patients characteristically have a high peripheral resistance (6).

While dysrhythmias may commonly occur in the recently transplanted heart, the incidence decreases in long-term survivors (7) and we saw none in our patient despite the additional predisposing effect of some coronary artery disease. It is of interest that patients with transplanted hearts develop coronary artery disease early, perhaps as a manifestation of a chronic rejection reaction (2). It is advisable to keep the rate-pressure product below 12,000 in the presence of coronary artery disease (14).

Since our only means to control rate and cardiac output was pharmacologic, dopamine (40 mcg/ml), isoprenaline (1 mcg/ml) and propranolol (1 mg/ml) were kept available. If the patient becomes hypotensive, having excluded hypovolemia (decreased preload) the drug of choice is dopamine which has a predominantly inotropic effect (15). Isoprenaline is more useful for its positive chronotropic effect on the denervated heart (9).

Preoperative cardiovascular assessment should include review of recent cardiac catheter data and angiocardiogram. These were made available to us. If possible, an echocardiogram and an exercise tolerance test should also be performed. These latter tests have the added advantage of being noninvasive and yet can yield valuable information.

The second major problem is that of abnormal immunologic status. Infection accounts for more than 50% of the deaths in these patients and so all possible causes should be avoided (2).

Infection by opportunistic or other organisms may be reduced by pre- and postoperative isolation and reverse barrier nursing. Intubation should be performed with sterile precautions and the orotracheal route is preferable to the nasotracheal since the latter is associated with infection by diphtheroids and staphylococcal commensals from the nasopharynx and skin (16, 17).

Since the cardiovascular status was good, we avoided invasive monitoring. We would have considered arterial, central venous and Swan Ganz catheters to be indicated if the LVEDP (resting or postangio) had been significantly elevated or if the echocardiogram had been abnormal.

Urinary catheterization was also avoided since this is associated with significant risk of infection. Antibiotic prophylaxis should be with bactericidal drugs.

The third challenge to the anesthesiologist is that of possible drug interactions. The problems of steroid therapy are well known and steroid cover is needed. Osteoporosis and aseptic necrosis of the femur is not uncommon in transplant patients and care should be taken to avoid pathologic fracture. Aspirin and dipyrimadole may cause bleeding intra- and postoperatively, and so should be stopped preoperatively and clotting mechanisms checked.

Azathioprine (Imuran) has been reported to antagonize the competitive neuromuscular blockers by its phosphodiesterase inhibiting properties (18), therefore larger doses of relaxants may be required. If possible, neuromuscular blockade should be monitored so that excessive doses of curare or pancuronium may be avoided.

Correct fluid replacement could be a problem in the absence of invasive monitoring. Thus, adequate preload is needed to maintain cardiac output, though large fluid volumes are contraindicated in the absence of a urinary catheter.

Although we chose to use neuroleptanesthesia for our patient, perhaps the most commonly described technique of general anesthesia for these patients is N_2O/O_2/narcotic/relaxant with low doses of a volatile agent (19), even though the latter may depress myocardial contractility.

There is an increased likelihood of deep vein thrombosis and pulmonary embolism in this instance, associated with the prolonged recumbency and neurologic deficit in the lower limbs. Despite the unfortunate outcome, we consider this case instructive because of the smooth nature of the two anesthetics undergone by this patient.

In conclusion, we have reviewed the special problems of the heart-transplanted patient undergoing major noncardiac surgery. Smooth, safe anesthesia is contingent upon careful preoperative assessment which may also reduce the need for invasive monitoring with all its attendant risks.

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Effect of Cis-diamminedichloroplatinum Chemotherapy on the Survival of Patients with Advanced Ovarian Cancer

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Introduction

The first controlled trials of cis-diamminedichloroplatinum (II) (DDP) for the primary treatment of advanced ovarian cancer were conducted at The Mount Sinai Hospital in 1974–1975 (1–3). These trials were expanded with the collaboration of our associates at Beth Israel Hospital and demonstrated a significantly better, 80%, objective response rate ($p = .01$) for combination chemotherapy with DDP and Adriamycin (ADM) than for standard therapy with ThioTEPA, 36%, or the 31% response rate for DDP alone (2, 3).

The study described in this report was undertaken because the randomized Phase II trial also demonstrated strong preliminary evidence that DDP delayed progression of residual tumor and increased survival compared to standard treatment (4–6). A Phase II study by design usually has too few patients to demonstrate statistically significant differences in survival due to treatments. This analysis was the best available method of both increasing the data base and examining the concurrent nonrandomized patients to detect possible flaws in study design due to selection of patients. The participating physicians refused to continue the randomized trial to accrue additional patients because they were convinced that standard treatment was inferior to the DDP-Adriamycin combination which produced a superior objective response rate and several surgically proven complete remissions. Additional nonrandomized patients were available for evaluation because several chemotherapists and patients considered DDP as an investigational drug that produced more nausea and vomiting than standard therapy and therefore they refused therapy.

The following report examines the results of treatment for all patients with a new diagnosis of disseminated ovarian cancer at The Mount Sinai Hospital during the time of the initial studies. The results support the conclusion that DDP combinations improve both progression-free and overall survival compared to standard therapy.

Materials and Methods

The records of all patients with initial surgery and early (six weeks) postoperative chemotherapy for biopsy-proven Stage III or IV ovarian cancer from December 1974 to June 1975 were collected from The Mount Sinai Hospital Tumor Registry. Patients were divided into four groups: controlled trials with standard chemotherapy or experimental chemotherapy; and patients with standard or experimental therapy not randomized to the trial. The experimental chemotherapy consisted of DDP 50mg/M^2 given as an IV bolus every three weeks with or without Adriamycin (ADM) 50 mg/M^2 as an IV bolus or triethylene thiophosphoramide (Thio TEPA, TSPA) 10 mg/M^2 IV day 1 and 2 of each three-week cycle. Standard therapy in the protocol consisted of TSPA 10mg/M^2 IV on day 1-4, and then once weekly and Methotrexate (MTX) 2.5mg po t.i.d. for four days at monthly intervals. Patients treated off protocol were

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treated with the same TSPA/MTX regimen or Melphalan with or without the later addition of 5-Fluorouracil and Cyclophosphamide as previously described by Smith et al (5) and Greenspan (6). Specific methods of giving intravenous fluids to prevent the nephrotoxicity of DDP are described in earlier reports (2, 3, 7). Patients treated with DDP regimens as initial therapy were only treated for ten to 12 cycles and then treated with a standard alkylating agent because the safety of cumulative therapy beyond ten to 12 cycles of DDP was unknown. The standard alkylating agent was started earlier if there was treatment limiting toxicity caused by DDP or progression of the tumor. Patients' records were evaluated for: survival, time to progression, change of chemotherapy, and effect of second therapy on overall survival. All patients were included in the analysis.

Results

There were 31 patients treated with standard therapy and 31 patients treated with DDP alone or in combination with other drugs. Survival was compared for each group with and without including patients who expired within three months of diagnosis (Table I). Twenty-five percent of patients treated with standard therapy died within two months, or within seven months excluding early deaths, compared to 17 and 18 months for patients treated with DDP. The median survivals were 11/12 months (unadjusted/adjusted for early deaths) vs 24/27 months and the 75th percentiles of survival were 15/15 months and 36+/44+ months. Only two patients treated with standard therapy are alive without progression three years after starting therapy while eight treated with DDP alone, or in combination, are alive (Table I). Among patients treated with DDP, only those treated with 300 mg/M^2 or more of DDP were among long-term survivors. The survival of nonrandomized patients with standard therapy is identical to the results of standard therapy in the controlled trial both at Mount Sinai and in the combined Mount Sinai/Beth Israel experience after patients with early deaths are excluded (3).

The results of crossover therapy were compared. There were no responses (0/4) to TSPA/MTX after objective (progression of disease) failure of a DDP regimen. There were five responses (5/11) to DDP regimens after objective failure of standard therapy. Each of these five responses added 12 months or more to survival for the individual patients and increased both the median and the 75th percentile survival attributed to standard therapy. It was not possible to treat additional patients with DDP after standard therapy because they became too sick for additional therapy.

Discussion

DDP alone or in combination doubled the median (24 vs 11) and the 75th percentile of survival (36+ vs 15 mo) and increased disease (progression) free survival at three years (8 of 31 vs 2 of 31). Standard treatment produced identical survival for randomized and nonrandomized patients. These results confirm the findings of the controlled trial and demonstrate that the superiority of platinum combination chemotherapy for patients with advanced ovarian cancer is not due to selection of patients.

The findings of the present study support our initial experience with the DDP regimens (2, 3). Results demonstrate that DDP regimens produce better survival than standard therapy. They also demonstrate that standard therapy produces equally poor survival in both our controlled trial and in our general patient population with newly diagnosed Stage III-IV ovarian cancer even after

TABLE I

Comparison of Survival Following Conventional and Cis-platinum Chemotherapy for the Postoperative Treatment of Newly Diagnosed Disseminated Ovarian Cancer

	Ovarian Cancer Stages III-IV Survival (months)			
			Survival "guarantee" 3 months[a]	
	Standard Combinations	Platinum Combinations	Standard Combinations	Platinum Combinations
No. of Patients	31	31	24	30
25th Percentile	2	17	7	18
Median	11	24	12	27
75th Percentile	15	36+	15	44+
No. Alive, 3 Years	2(06%)	8(26%)	2(08%)	8(27%)

[a] Excludes all deaths within three months of primary surgery.

adjustment for early deaths. In large trials TSPA/MTX and Melphalan produce nearly identical response rates and survival (4–6, 8) similar to those determined from our Tumor Registry files and in our controlled trial (1–3). ADM alone or in combination with standard alkylating agents does not produce better survival than standard therapy (6, 9).

There is as yet no clear difference between the DDP regimens, although the DDP-ADM regimen strongly tends to produce the best response rates with the least toxicity. New three- and four-drug regimens first developed in our institution appear promising (10, 11). Similar regimens have been tested by other investigators who report early results similar to our own (12–14), but these regimens are not yet clearly established to be better than DDP-ADM.

The DDP regimens appear to almost eliminate the appearance of early disease progression. Only five of 31 patients died in the first year, and the 25th percentile of survival was 17 months. Response and survival appear to be uniquely independent of tumor grade compared to standard and experimental regimens (15, 16) in that patients with poorly differentiated tumors do well (3, 13). Surprisingly, there was no apparent relationship between the size of the residual tumor and the chance of producing a complete clinical or pathologic remission in this and subsequent studies (17).

This study supports our earlier reports (3) that DDP-containing regimens (where patients are treated with 300mg/M^2 or more of DDP) may produce prolonged survival and that the frequency of 3+ years progression-free survival may increased 4-fold compared to standard therapy.

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The Effect of I.V. Injection of Small Amounts of Calcium on Gastric Secretion and Gastrin Hormone in Patients Suffering from a Duodenal Ulcer

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Abstract

The influence of calcium upon the gastric secretion as well as on serum gastrin levels is studied in detail.

Twenty ml of calcium gluconate were injected in nine patients suffering from a duodenal ulcer. In five other patients serving as a control group, the same parameters were studied after an intravenous (I.V.) injection of 20 ml of normal saline. Injection took approximately ten minutes with an average of 2 ml per minute.

A statistically significant rise of the acid secretion was observed during the first and the second hour from the end-time of the injection. Gastrin levels in the blood serum were found statistically higher than normal, in 30 and 60 minutes time, after the calcium gluconate application, while in the 120 minutes time the difference between the gastrin levels was found to be not statistically important. Injection of normal saline in five patients serving as a control group failed to change the production of hydrochloric acid as well as the gastrin levels in blood serum.

Our findings suggest that the best available explanation on the mechanism involved through which calcium influences gastric secretion is the level of the gastrin itself.

Introduction

The influence of induced hypercalcemia upon the gastric secretion has been studied a) in normal individuals (1–3), b) in patients suffering from a gastroduodenal ulcer (4), and c) in those with the Zollinger-Ellison syndrome (5, 6).

This study investigates the influence of intravenous injection of small amounts of calcium gluconate upon the acid secretion, serum gastrin and serum calcium levels in patients with duodenal ulcer.

Materials and Methods

Fourteen volunteers, suffering from a duodenal ulcer (12 males and two females), were studied in detail. Confirmation was achieved by x-rays and endoscopy. Before the test, the patients were examined to rule out cardiac, renal metabolic diseases, and especially hyperparathyroidism. In nine patients (eight males, one female), calcium was intravenously injected, whereas in the other five (four males and one female) who served as the control group, normal saline was administered. The age of the patients of the first group was between 41 and 62 years with an average age of 49.6, while the age in the control group ranged between 44 and 56 years with an average age of 48 years.

The test was performed in the morning, after a twelve-hour fasting and avoidance of medication influencing gastric secretion.

Gastric secretion was collected by continuous suction via a radiopaque nasogastric catheter, secured uncoiled along the greater curvature of the stomach. The stomach was emptied of its contents, after which basal secretion was collected for

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60 minutes. Then 20 ml of 10% calcium gluconate (180 mg of Calcium) was injected I.V. during a period of 10 minutes.

Gastric secretion produced during the 10 min injection time was discarded, after which gastric juice was collected for two hours.

Blood samples were collected from the basilic vein via a thin polythylene catheter 60 min before, at zero (0) time and 30, 60, and 120 min after the injection. Zero time corresponds at the beginning of the injection; the 30 min sample was the sample collected 30 min after the end of the injection time.

Basic calcium and gastrin values in blood serum are considered the mean values found at 60 min before and at the zero time of the test.

Concentrations of acid were calculated in mEQ/L (each sample is titrated with an N/10 NaOH solution to pH 7.0−7.4, using as indicator phenol red). The total amount of acid in mEq of each sample (mEq/h) was calculated as the product of its volume and concentration. Serum gastrin measurement was done by radioimmunoassay (7) with Squibb reactives, obtained from the Gastrin Immutore KIT (No $I_{3\text{-}279}$). Serum calcium levels (total calcium) were measured by titration with E.D.T.A. (8). Statistical analysis of the results was assessed using t-test (Student's-test) (9).

Results

There was no statistically significant ($P > 0,10$) difference in age, basal acid secretion, blood calcium and gastrin values between the patients subjected to injection with calcium gluconate and those injected with normal saline.

Acid secretion: After an injection of calcium, a statistically significant ($P < 0,01$) increase of hydrochloric acid secretion was observed. One patient did not respond to the calcium stimulus during the first hour and another one during the second hour (Fig. 1).

There was no statistically significant change ($P > 0,10$) in the secretion of hydrochloric acid after the injection of normal saline (Fig. 2).

Gastrin: A statistically significant rise in blood gastrin levels was observed 30 minutes ($P < 0,01$) and 60 minutes ($P < 0,05$) after the injection of calcium, whereas the observed rise 120 minutes after the injection was not statistically significant ($P > 0,10$). No statistically significant rise ($P > 0,10$) was observed 30, 60, and 120 minutes after the injection of normal saline in the control group (Fig. 3).

Calcium: A statistically significant rise of the

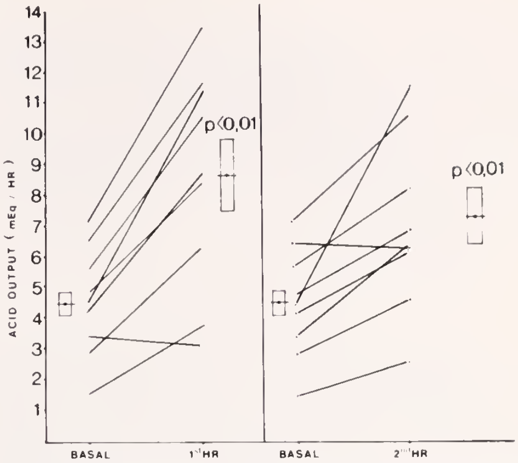

FIG. 1. Secretion of hydrochloric acid during the first and second hour following I.V. injection of calcium, in each of the nine patients is compared with basal secretion.

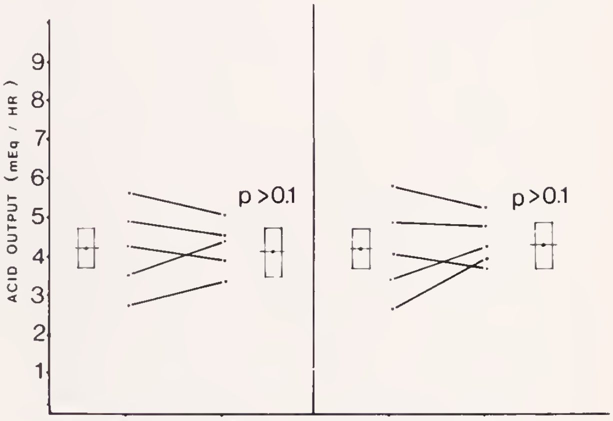

FIG. 2. Secretion of hydrochloric acid during the first and second hour after the intravenous injection of normal saline in each of the five patients is compared with basal secretion.

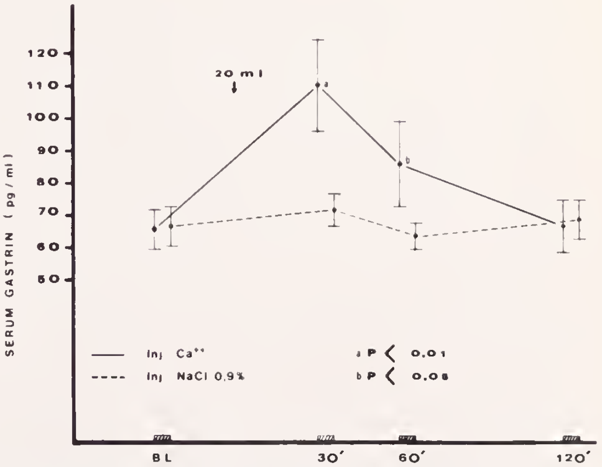

FIG. 3. Mean values of blood gastrin levels before and after the administration of calcium or normal saline.

blood calcium levels was observed 30 minutes (P < 0,01) and 60 minutes (P < 0,05) after the injection of calcium, whereas after 120 minutes the difference was not significant (P > 0,10).

In the control group, no significant change in the values of blood calcium was observed 30, 60, and 120 minutes (P > 0,10), after the injection of normal saline (Fig. 4).

Discussion

Recent advances in radioimmunology have made possible more detail studies of the mechanism and effect of serum calcium on gastric secretion. Radioimmunoassay has also made possible the detection of serum gastrin levels and thus the correlation of changes in gastric secretion after an induced hypercalcemia.

Various explanations concerning the mechanism of calcium action on gastric secretion have been reported (1, 3, 10, 11). In general, investigations up to now, accept that the rise of gastrin levels is the most important factor in induced hypercalcemia and gastric hyperfunction (12). Serum gastrin levels may rise by increased production and secretion of the antral mucosa, while gastrin duodenal secretion seems not to be influenced by induced hypercalcemia (13). A definite increase of the hydrochloric acid production has been reported after an intravenous infusion of calcium in normal individual as well as in patients suffering from a gastric ulcer (1–3, 14).

Previous published data of continuous infusion of calcium in patients with a duodenal ulcer are in accord with our results (4, 11, 15). In our study, a single injection containing small amounts of calcium produced the same end results as the continuous infusion.

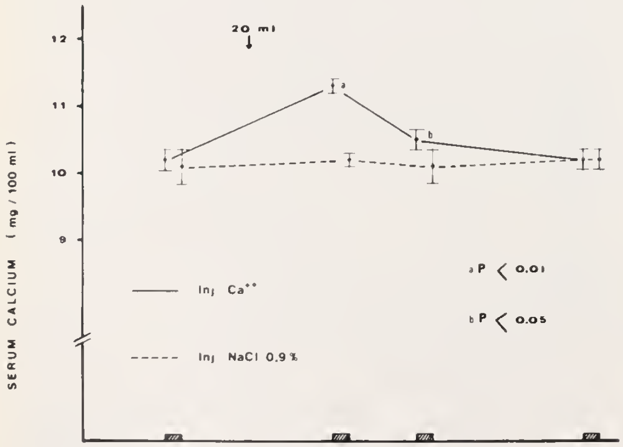

FIG. 4. Mean values of blood calcium before and after the administration of calcium or normal saline.

The above findings suggest that calcium containing drugs administered to patients suffering from peptic ulcer should be carefully scrutinized for their possible induction of gastric hyperacidity.

Conclusions

Intravenous injection of 20 ml of a 10% solution of calcium gluconate, that is, a total of 180 mg of calcium, administered over 10 minutes, in patients suffering from a duodenal ulcer, caused:

1) An increase in the secretion of hydrochloric acid, during the first and second hour after injection.
2) An increase of the serum gastrin levels during the first hour after the injection, whereas at the end of the second hour the levels returned close to the normal.
3) An increase of the total blood calcium during the first hour after injection, which at the end of the test returned to normal.

Our view in accordance with others, is that the rise of the gastrin levels is responsible for the increase of the secretion of hydrochloric acid. The above however does not exclude the possibility that the increase of serum gastrin levels and gastric acid secretion are parallel but independent responses to calcium stimuli.

Calcium containing drugs, administered to patients suffering from a peptic ulcer, should undergo a further study as far as their therapeutic value is concerned.

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Fusiform Aneurysm of the Superior Vena Cava

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Abstract

A case of fusiform aneurysm of the superior vena cava in a 16-year-old white male is presented. The diagnostic procedures for this entity are discussed and the literature is reviewed. In addition, this is the first report in the literature that we are aware of that demonstrates this entity by computed tomography.

Introduction

Aneurysm of the superior vena cava is certainly a rare entity. A review of the English literature reveals only 3 sacular (1–3) and 8 fusiform (4–11) aneurysms reported. We recently observed a patient who presented with trauma and subsequently was shown to have a fusiform aneurysm of the superior vena cava demonstrated both by angiography and computer tomography. Aneurysms of the superior vena cava must be considered in the list of superior mediastinal masses.

Case Report

This 16-year-old white male sustained trauma to his head and sacral spine and was admitted for observation. Past medical history revealed a fracture of the right clavicle at age two and of the left clavicle at age 12. Social and family history were unremarkable. The review of systems revealed a recent sore throat. On examination, he was alert and oriented. The blood pressure was 120/74. There was a laceration of the forehead. Multiple, slightly tender lymph nodes in the cervical region were noted. The examination of the throat was normal. Pertinent laboratory values included a white blood count of 12,000 and a positive mono spot test. PA film of the chest revealed a smoothly marginated mass in the right paratracheal region (Fig. 1). The mass was not seen on the lateral view. At fluoroscopy, the size and shape of the mass changed during Valsalva maneuver (Fig. 2). An esophagram was normal. Contrast was then injected into both antecubital veins demonstrating fusiform dilatation of the superior vena cava and right bracheocephalic vein (Fig. 3). A small amount of contrast refluxed into the external jugular vein. The lumen of the superior vena cava below the dilatation was normal in calibre with no evidence of obstruction. There was no mass in the right atrium. A CT scan was performed to rule out the possibility of other mediastinal pathology (Fig. 4). The aneurysm was enhanced greatly following the injection of contrast material indicating the vascular nature of this lesion.

Discussion

In 1950, Abbott described the first case of fusiform aneurysm in an asymptomatic male college student (4). The diagnosis was suspected but the patient was operated upon and the aneurysm was wrapped with cellophane in hopes of preventing rupture. A second aneurysm was reported five years later by Lawrence. This was the first report of a sacular aneurysm. It arose from a stalk and was successfully resected. That patient presented with thoracic spine pain and dyspnea and was the only case in the literature in which there were symptoms. Presumably, the symptoms were unrelated to the aneurysm. Two other cases of sacular aneurysm have been reported and have been successfully resected as well (1, 2). All the other cases that have been reported have been fusiform in configuration.

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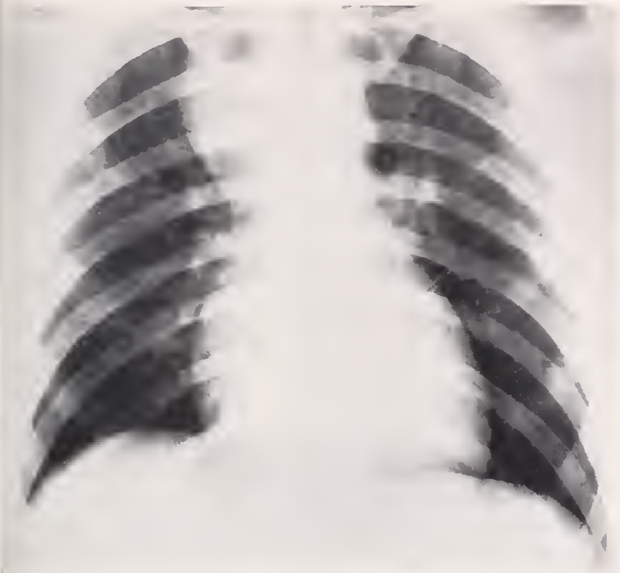

FIG. 1. PA film of the chest reveals a large right paratracheal mass.

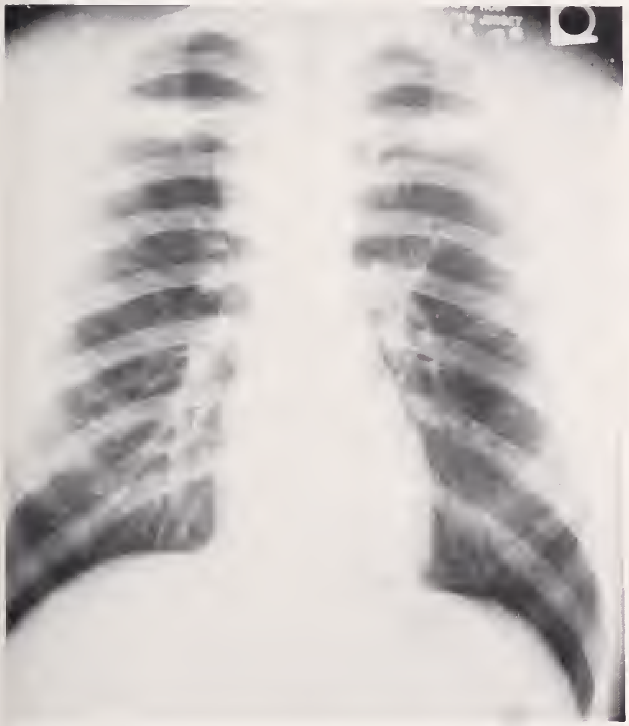

FIG. 2. Upright film of the chest, obtained during Valsalva maneuver reveals significant decrease in the size of the mass.

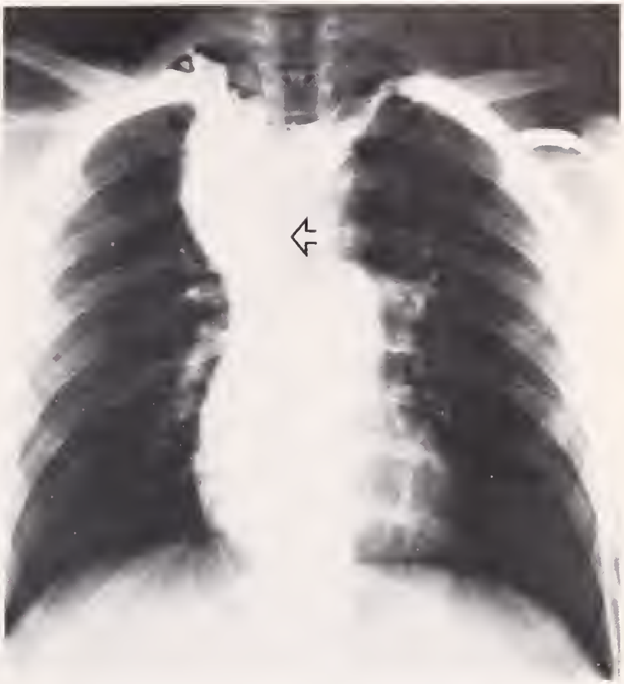

FIG. 3. Venous angiogram demonstrates the aneurysm of the superior vena cava (arrows).

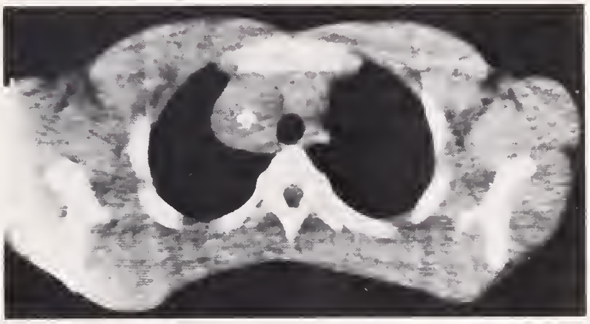

FIG. 4. CT scan prior to contrast injection reveals a mass in the right paratracheal region with a smooth margin. Following contrast injection, there was marked enhancement.

Although these vascular lesions are rare, they manifest characteristic features. It is therefore distressing that the diagnosis was considered initially in only two of the eight patients (4, 10). Thoractomy was performed in four patients following an extensive evaluation that included bone marrow aspiration, bronchoscopy, mediastinal tomography and thyroid scanning. Needle aspiration was almost attempted in one patient (7–9, 11).

Therefore, use of fluoroscopy, or at least supine and upright films is almost imperative in evaluating paramediastinal masses to exclude vascular lesions. The vascular nature of our case and others like it becomes immediately obvious when a Valsalva or Muller maneuver is done. The diameter of the mass will change in size and shape when alterations in intrathoracic pressure are applied, for example, increased pressure during the Valsalva maneuver causes decrease in the overall volume of the lesion. The reverse is observed as the pressure decreases, during the Muller maneuver. Of greater diagnostic significance is direct opacification of the lesion by contrast material. This is demonstrable utilizing angiographic techniques or by enhancement following the injection of contrast on CT. The latter is developing into a common diagnostic procedure.

One interesting clinical feature is that our patient had cervical lymphadenopathy and a positive monospot test. Ream, in 1972, described a case of a 20-year-old female who also had mononucleosis (11). The similarity between our case and that of Ream's is striking. The possible relationship, however, between these two entities is unclear, if indeed, any relationship exists at all.

No attempt has been made to resect any of the fusiform aneurysms that have been reported. In one case, the aneurym was wrapped with cellophane (4). In the other three that were discovered at surgery, the chest was closed when the mass was seen to be an aneurysm. The superior vena cava is a low pressure system with vents at both its upper and lower borders and, therefore, fusiform aneurysms should not be subject to sudden rupture. We concur with the conservative approach in the literature and elected to observe our symptomatic patient with serial chest films.

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Pancreatitis in Renal Transplant Recipients: A Report of Three Cases

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Abstract

Pancreatitis has been reported to occur in 2%–6% of renal allograft recipients. Pancreatitis complicating the course of an immunosuppressed patient carries a high incidence of morbidity, and is frequently lethal. The evidence, however, of cause-effect relationship between renal transplantation and pancreatitis has remained incomplete and inconclusive. Analysis of the clinical course of three patients among our allograft recipients who developed pancreatitis is presented.

Kidney transplantations were performed using standard surgical technique. Immunosuppression was maintained with high doses of Prednisone which are rapidly tapered to a maintenance dose of ½ mg Prednisone per kilo per day, and Azathioprine of 1–1½ mg per kilo per day. When the diagnosis of pancreatitis was made, oral Prednisone and Azathioprine were discontinued, and Prednisolone and Cyclophosphamide were administered to maintain immunosuppression.

Case Report

Case I: P.S., a 33-year-old, Black male, was admitted to the Transplant Unit with the diagnosis of acute pancreatitis. Two years earlier, he underwent a successful cadaveric kidney transplant for end-stage renal diseases, secondary to heroin nephropathy. He also had a history of alcohol abuse, as well as a history of alcoholic pancreatitis five to eight years prior to this admission. Additionally, his past history included gouty arthritis treated with Colchicine, as well as a bout of infectious hepatitis. All oral intake was discontinued, and he was treated with intravenous fluid and hyperalimentation with gradual improvement. Three weeks after admission, he developed an episode of upper gastrointestinal bleeding from gastritis requiring transfusion of three units of blood. Five weeks following admission, an exacerbation of abdominal pain associated with high fever developed. Abdominal sonogram showed an increase of a previously known cystic lesion of the pancreas. Total parenteral nutrition was administered, and abdominal exploration was performed, draining an infected pancreatic pseudocyst containing 700 cc of cloudy fluid. The patient had no postoperative complications, and he was able to tolerate oral intake two weeks following the abdominal exploration. Renal function remained stable, and he was discharged on maintenance doses of oral Prednisone and Cyclophosphamide.

Case II: M.N., a 38-year-old, hypertensive, Black female, was admitted to the hospital with acute pancreatitis one and a half years after cadaveric kidney transplantation. During the posttransplant period, she required Orinase for control of diabetes mellitus which had developed following the kidney transplant. Pertinent past history included cholecystectomy for cholelithiasis done eight years prior to this admission. The patient was treated with total parenteral nutrition, antibiotics and nasogastric suction. Gradual clinical improvement occurred in the ensuing three weeks. Serial sonograms and CT scan showed an enlarging pancreatic mass that was partially cystic. Intravenous cholangiography showed a faintly visualized, but nonobstructed biliary tree. Surgical exploration revealed extensive pancreatitis. Intraoperative cholangiogram showed no common duct stones. Postoperative course was characterized by extremely slow recovery, without complete resolution of symptoms. Six

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weeks following the first operation, the patient again became afebrile, and developed left upper quadrant pain. Sonography showed a new cyst in the spleen for which a second exploration was performed, draining an infection pseudocyst. The patient expired two days later in pulmonary edema. No autopsy was obtained. Renal function remained stable throughout the course of the hospitalization.

Case III: P.S., a 41-year-old, Black male, with a longstanding history of hypertension and chronic renal failure, underwent a routine cadaveric kidney transplant. Following transplant, he remained anuric for two weeks, following which the kidney started to function. Two weeks later, however, acute rejection developed necessitating removal of the allograft. One month after the transplant nephrectomy, he developed abdominal pain, elevated serum amylase, and the clinical picture of acute pancreatitis. Sonography showed a pancreatic mass which was partially cystic. The patient was treated with intravenous antibiotics and total parenteral nutrition for a period of six weeks with complete resolution.

Discussion

Pancreatitis has been reported to occur in approximately 2%–6% (2, 6, 8) of renal transplant recipients. Many factors seem to contribute to the development of pancreatitis in these complex clinical settings. Inflammatory changes of the pancreas have been reported not uncommon in uremic patients per se (3, 4). Mechanical trauma to the pancreas may occur at the time of renal transplantation when a concommitant splenectomy or a left nephrectomy is performed as well (5, 6). Medications which are administered routinely to these patients, steroids, Azathioprine and diuretics, have all been known to precipitate acute pancreatitis (7, 8). Diabetes, alcohol consumption, secondary hyperparathyroidism may all contribute separately, or in combination to account for the increased incidence of these rather serious complications of kidney transplantation. There seems to be no definite relationship between the steroid and Azathioprine, and the occurrence of pancreatitis (9–12).

When pancreatitis does develop, the use of parenteral nutrition, nasogastric suction, intravenous antibiotics, as well as Prednisone and Cytoxan, allows for clinical management of these patients while maintaining allograft function. Surgery is indicated if there is evidence of pancreatic abscess formation, or the development of nonresolving pseudocyst.

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The Role of Insufficiency of the Sphincter of Oddi in the Pathogenesis of Pancreatitis

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In a previous investigation, the technique of producing incompetency of the Sphincter of Oddi and the effects of this incompetency on the pancreas were studied in canines. Initially, synthetic tubes of small diameter (1–1.5 mm) were fixed in the main pancreatic duct (1). These tubes frequently became blocked by mucus plugs, which often led to pancreatic fibrosis. With cannulas of larger diameter (2–2.5 mm), it was possible to produce insufficiency of the Sphincter of Oddi. These tubes did not become blocked and permitted free reflux of duodenal contents into the pancreatic duct.

This study reports the alterations in pancreatic blood enzyme concentrations as well as the morphologic changes in the pancreas induced by experimentally constructed incompetency of the Sphincter of Oddi in the dog.

Protocol

Twenty dogs weighing between 30–40 lbs were used in this investigation. In 11 animals, a synthetic cannula, 2–2.5 mm in diameter, was fixed in the main pancreatic duct in such a way as to extend through the Sphincter of Oddi into the duodenum and permit free communication between the duct and duodenum, that is, incompetency of the Sphincter of Oddi. In seven dogs, the main pancreatic duct was doubly ligated, transected, and the cut ends of the ducts separately isolated by embedding in the omentum. Two healthy dogs served as controls undergoing sham operations.

Pancreatic enzyme concentrations were determined in the blood prior to surgery and sequentially afterwards. Amylase concentrations were obtained by the Smith-Roe method (2); trypsin and trypsin inhibitor levels were analyzed according to Erlanger-Schaternikoff (3).

After 30 days, the dogs were sacrificed. Small pieces of pancreas were immediately removed from the head, body, and tail of the pancreas and fixed in 10% formalin, in Karnua solution, and embedded in parafin. The histologic sections were stained with hematoxylin-eosin, Van Geson-stain for connective tissue and with orcein for elastic fibers. Cellular RNA and DNA were determined by Brashe and Felgen tests; nonspecific cellular esterases were estimated by Homary method; and Zymogen granules stained with Mallory solution.

The method of variational statistics was applied to analyze the obtained biochemical data (4).

Results

Tables I and II present the sequential blood trypsin, trypsin inhibitor, and amylase concentrations expressed in units and milliunits before and at 10, 20, and 30 days after surgery producing odditic incompetance or pancreatic ductal ligation in the animals.

The blood amylase levels in both the study and control group became progressively elevated. In the animals with insufficiency of the Sphincter of Oddi, this increase was statistically significant and reached 2872 units/cc by the 30th day. In the control animals the amylase elevation attained a peak at 10 days, 9056 units, and then declined to 4512 units.

The average serum trypsin value, initially 1.7 milliunits/cc in the dogs with odditic incompetence, peaked on the tenth day at 7.5 milliunits/cc and thereafter decreased to 4.4 milliunits/cc on the

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TABLE I

Pancreatic Enzymes in Dogs Before and After Surgery
Pancreatic Duct Cannulation (Odditic Incompetence)

	Before Operation	After operation		
		10 days	20 days	30 days
		Amylase (Units/cc)		
Mean	1430	2512	2119	2872
SD	870	1015	710	960
n	11	11	11	11
t	—	1.878	1.417	2.579
p	—	>0.05	>0.10	<0.002
		Trypsin (Milliunits/cc)		
Mean	1.7	7.5	5.2	4.4
SD	1.6	6.4	5.0	5.7
n	11	11	11	11
t	—	2.147	1.590	0.450
p	—	<0.05	>0.10	>0.10
		Trypsin Inhibitor (Milliunits/cc)		
Mean	415	340	374	390
SD	80	117	73	90
n	11	11	11	11
t	—	1.229	0.891	0.490
p	—	>0.10	>0.10	>0.10

TABLE II

Pancreatic Enzymes in Dogs Before and After Surgery
Pancreatic Duct Ligation

	Before Operation	After operation		
		10 days	20 days	30 days
		Amylase (Units/cc)		
Mean	2352	9056	1480	4512
SD	1090	8800	140	3120
n	7	7	7	7
t	—	1.865	1.495	1.234
p	—	>0.05	>0.10	>0.10
		Trypsin (Milliunits/cc)		
Mean	3.5	3.8	5.2	8.8
SD	1.8	3.1	1.1	5.2
n	7	7	7	7
t	—	0.166	1.555	2.003
p	—	>0.10	>0.10	>0.05
		Trypsin Inhibitor (Milliunits/cc)		
Mean	491	340	320	425
SD	136	164	107	31
n	7	7	7	7
t	—	1.411	1.987	0.956
p	—	>0.10	>0.05	>0.10

thirtieth day. In the duct ligated dogs, the initial average trypsin concentration rose progressively to 8.8 milliunits/cc by the 30th day.

In neither the canulated nor the ligated animals did the operative procedure result in significant change in the blood trypsin inhibitor concentration.

All other biochemical tests (blood sugar, cholinesterase, transaminase (SGOT and SGPT), aldolase, cholesterol, blood protein concentrations) showed no statistically significant alterations from preoperative values.

The gross appearance of the pancreas in the sacrificed animals with odditic incompetance was no different from the control animals. On section, the tissue was slightly moist but the architecture was normal. On microscopic section the following changes were noted in the interacinar connective tissue of the odditic incompetent canines: edema, venous congestion, hemorrhagic areas, and infiltrations of lymphocytes, polys, and few plasma cells in the periphery of the acini (Fig. 1a). Occasional acini exhibited stromal inflammation. No increase of inter- or intraacinar connective tissue and no deformation of acini was seen. The acinar cells appeared to be functioning normally. The ribonucleoproteins were found as a wide pyroninophilic margin in the basal parts of the acinar cells (Fig. 1c). Nuclear chromatin was uniformly distributed within the nucleus. There were no secretory-cycle disturbances. Mallory stain revealed numerous zymogen granules located in the apical parts of the acinar cells around secretory canaliculi (Fig. 1e). The activity of nonspecific esterases in the cytoplasm of acinar cells was prominent (Fig. 1f). The argyrophilic stroma and the elastin of blood vessels were normal. The epithelial layers of the ductules were normal with clear cylindrical epithelial cells, the apical part of which contained PAS-positive material. Areas of local cellular infiltration were noted in the periductal connective tissue. The above morphologic changes in the pancreas are characteristic of minimal acute pancreatitis.

The pancreas of animals with ligated ducts microscopically at time of sacrifice appeared atrophic and indurated; on section, the tissue was pale and granular. Microscopic preparations revealed disorganization of acini resulting from connective tissue deposits in and around them (Fig. 1b). Blood vessels and intraacinar ductules were reduced and missing in some acini while in others they were found in the connective tissue of the stroma. The acinar cytoplasm was clear with some vacuolization. Nuclear chromatin was not uniformly distributed in carioplasm but was concentrated in small aggregates. The content of RNA was substantially reduced with ribonucleoproteins distributed uniformly in the basal parts of cells (Fig. d). There was a significant decrease in nonspecific esterase activity as well as in the secretory function of the acinar cells. The zymogen granules in the apical parts of acinar

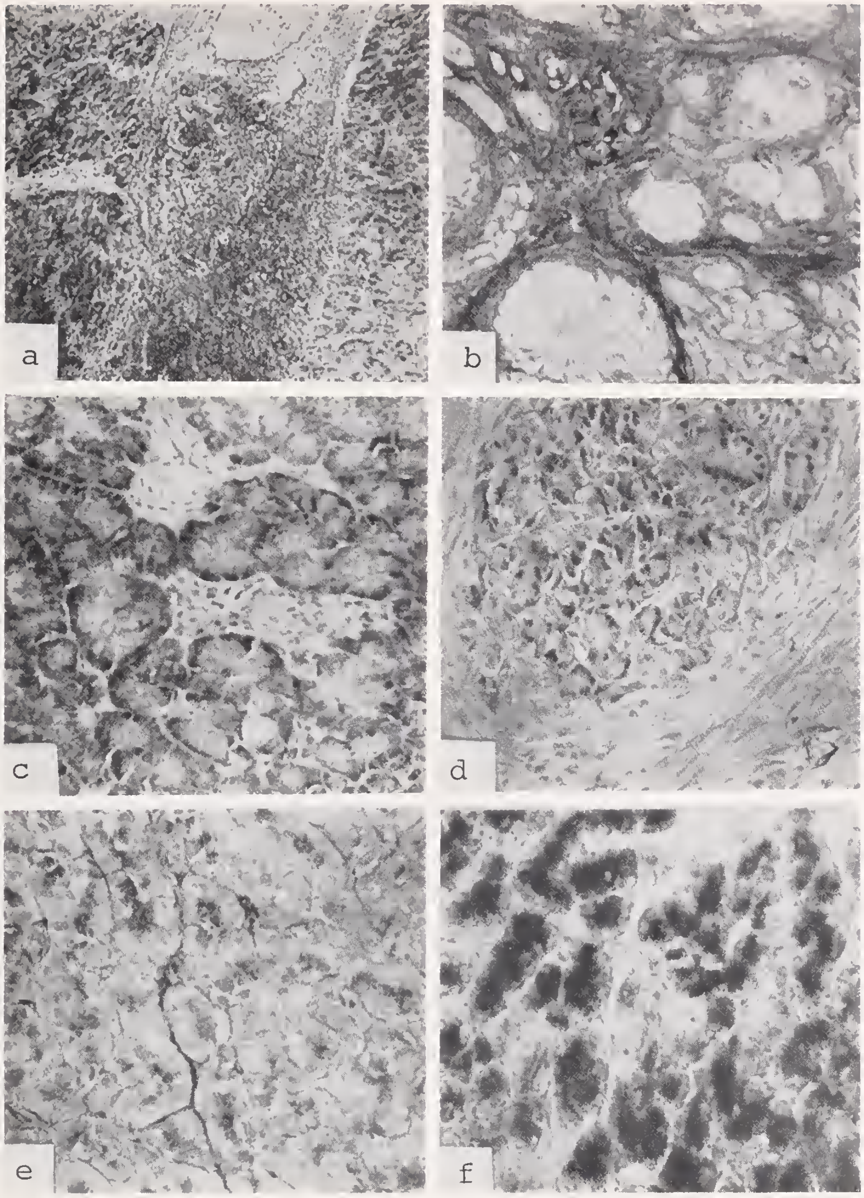

FIG. 1. Morpholigic changes in the pancreas after ligation and cannulation of the pancreatic ducts. a) Inflammation in the interlobular connective tissue: plethors of veins (H & E). b) Cirrhotic changes in the pancreas (Van Gison). c) RNA in the basal zones of acinar cells (Brashe stain). d) Moderate decrease in RNA content in the cytoplasm of the acinar cells (Brashe stain). e) Zymogen granules in the apical zones of the cytoplasm in the acinar cells (Mallory stain). f) High activity of the nonspecific esterase in the cytoplasm of acinar cells (Homory stain).

cells were not numerous and were missing entirely in some cells. Some groups of cells contained a large polygonal nuclei occupying the greater part of the cytoplasm. These morphologic changes are characteristic of pancreatic fibrosis.

Discussion

The classical theory of etiology of pancreatitis, the Opie mechanism, hypothesized obstruction of the papilla of Vater by a gallstone, the conversion of the ampula into a "common channel" through which bile regurgitated into the pancreatic duct wherein it induced inflammation by activating proteolytic pancreatic ferments. Numerous objections to this hypothesis (5–10) resulted in frequent modifications (11–15) but none of these was in complete conformity with clinical observations and all failed to explain the reflux of bile from the common duct into the pancreatic duct against a pressure gradient. Some recent investigators (8, 19–21) have suggested that the activation of pancreatic ferments within its ductal system might result from regurgitation of duodenal contents such as emulsified fat (16–18) or kinase enzymes. Duodenal regurgitation has been observed during vomiting as well as in patients with incompetant sphincters.

The experimental findings support the ability of duodenal reflux through an incompetant sphincter to initiate pancreatitis. When the pancreas was protected by ductal ligation, fibrosis but not inflammation resulted. In a parallel clinical study (20), it was shown that injection of radiopaque dye (biligrafin) could be observed in the duodenum of patients with pancreatitis but not control subjects during the interdigestive phase. Of interest also is preliminary and unreported extension of our protocol which demonstrated the effect of placing canulas of different diameter through the papilla–the larger the diameter the more advanced the pathology–the range being from edema with small canulas to hemorrhagic necrois with larger tubes.

In general, the enzyme data correlated with the morphology. Blood amylase continued to rise in the animals with odditic insufficiency indicating persistent and continued inflammation. In the duct ligated canines, the blood amylase rose initially and then declined almost to control levels. Blood trypsin-like activity and trypsin inhibitor levels in general do not correlate with pancreatic pathology in man and failed to do so in this experiment, thus in accord with the data of other authors (22).

Summary

A plastic tube was inserted in the pancreatic duct causing sphincter of Oddi insufficiency in experimental dogs.

On the thirtieth day following the operation, the experimental animals developed acute pancreatitis with elevated blood amylase levels and morphologic changes in the pancreas.

The wider diameter of the cannula, the more prominent are the pathologic changes in the pancreas of the experimental animals. This parallelism was also noted in pancreatic patients with sphincter of Oddi insufficiency.

The second group of experimental dogs, those with ligated pancreatic ducts, developed cirrhosis of the pancreas. The serum blood amylase level increased after the operation but regressed by the end of the experiment.

Insufficiency of the sphincter of Oddi is a possible cause of pancreatitis.

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Inflammatory Esophagogastric Polyp Roentgen Features

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Introduction

The inflammatory esophagogastric polyp is a rare lesion that has a very characteristic appearance and location. The following case is presented to demonstrate this interesting lesion and to show how the roentgen features lead to a specific diagnosis in most cases.

Case Report

An 85-year-old white male was admitted to the hospital after an episode of dizziness associated with a cardiac arrhythmia. The patient was found to have a hematocrit of 33 and guiac positive nasogastric aspirate. His hematocrit continued to fall during the first few days of the hospitalization although he never experienced hematemesis or hematochezia. He had no symptoms of reflux esophagitis. He had been in good general health except for a lumbar sympathectomy for calf claudication five years earlier. He was a heavy cigarette smoker.

An upper gastrointestinal series was performed revealing an exquisitely smooth, mobile, 2–3 cm nonobstructing intraluminal mass predominantly in a moderate sized direct hiatus hernia (Fig. 1). Fiberoptic endoscopy was performed on the second hospital day. At 38 centimeters, a small hiatus hernia was noted. A polypoid lesion, 2 centimeters in diameter, on a broad pedicle arose from the esophageal side of the esophagogastric junction and prolapsed into the stomach. It appeared superficially ulcerated. The esophagus was normal. The polypoid lesion was removed via the endoscope.

Pathologic examination of the gross specimen revealed a polypoid mass 3 cm in diameter with a .5 cm diameter pedicle. The cut surface consisted of smooth myxomatous tissue, homogenously yellow-white with areas of hemorrhage, covered by a thinned mucosa. The microscopic diagnosis was an inflammatory fibroid polyp of the esophagogastric junction with eosinophilic infiltration. A biopsy specimen of the adjacent mucosa showed esophagogastric mucosa with chronic inflammation.

Discussion

Inflammatory esophagogastric polyp is an uncommon benign lesion of the esophagus occurring predominantly in men in the 20–68 year old group (1). The lesion has been described in children (2) and in women (3). The lesion has been variously referred to as inflammatory fibrous polyp, inflammatory fibroid polyp, and eosinophilic granuloma. Lesions of similar histologic type have been more frequently reported in the stomach, small bowel, and colon (4). Clinically, many of these patients present with symptoms of esophagogastric reflux although dysphagia and upper gastrointestinal bleeding have been reported (Table I) (3).

Pathologically, on gross examination, it appears as a polypoid submucosal lesion frequently with surface ulceration. Histologically, it is composed of fibrous tissue, fibroblasts, and reactive blood vessels. There is diffuse infiltration by inflammatory cells including varying proportions of eosinophils (3, 5).

The pathogenesis of the esophagogastric inflammatory polyp is not clearly delineated. It is generally felt to represent an inflammatory mass provoked by the presence of gastroesophageal reflux (1–3). It has also been suggested that it may represent a localized manifestation of eosinophilic infiltration of the gastrointestinal tract not as-

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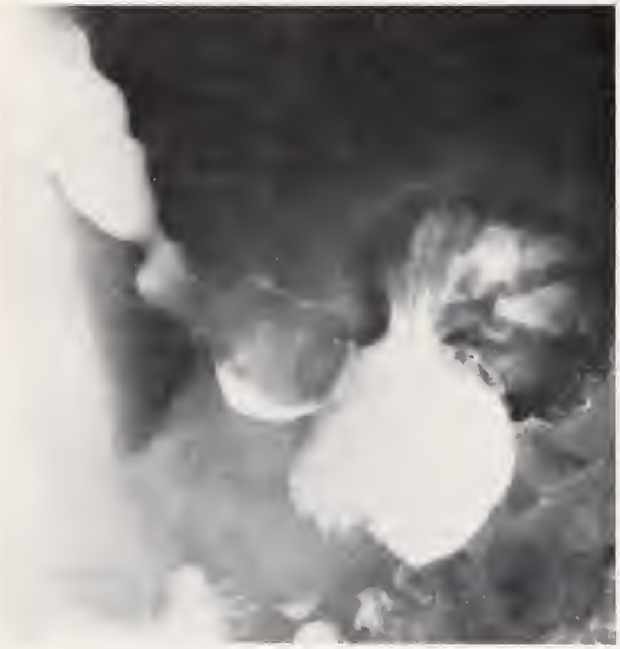

FIG. 1. Large, exquisitely smooth round filling defect within a moderate sized direct hiatus hernia. There is no discrete pedicle. There is no filtration of the adjacent wall of the esophagus or stomach. There are no focal collections of barium within the lesion to suggest ulceration. Tertiary contractions are evident in the distal esophagus.

sociated with blood eosinophilia or hypersensitivity (5).

Radiographically, this type of inflammatory polyp occurs characteristically at the esophagogastric junction and is easily identified. It appears as a smooth round moderate sized filling defect with or without a discrete pedicle. It may sit atop a prominent mucosal fold which tapers into the stomach (1). The lesion is mobile and may be seen, at fluoroscopy, to prolapse into the stomach. There is never evidence of infiltration of the adjacent wall of the esophagus. There may be focal collections of barium within the lesion representing mucosal ulceration. Hiatal hernia and tertiary contractions of the esophagus have been frequent associated findings. Obstruction has been reported in one case. However, this lesion was atypical in location occurring several centimeters above the esophagogastric junction and was unusually large measuring 5 × 3.5 cm (6).

Other lesions may present as polypoid masses in the esophagus and require differentiation from the inflammatory polyp. These lesions include the fibrovascular polyp which usually occurs in the upper third of the esophagus and is usually on a long stalk (7). The most common benign submucosal tumor of the esophagus is the leiomyoma. The leiomyoma has characteristic radiographic findings but rarely may assume a polypoid configuration within the lumen (8, 9). A foreign body, especially a bolus of solid food, may appear as a filling defect but is usually smaller and more irregular and impacts at a point of narrowing of the lumen. Rarely, primary malignant lesions of the esophagus such as squamous cell carcinoma, pseudosarcoma, carcinosarcoma and melanosarcoma may present as polypoid lesions but are easily differentiated radiographically by their irregular outline, associated contour defect and prominent ulceration (10). They are also easily differentiated histologically. Metastatic hypernephroma to the esophagus presenting as a polypoid mass has been reported.

TABLE I

Year	Author/Title	Patient	Presentation	Diameter of Polyp
1962	Schreiber: Granuloma E-G junction with eosinophilic infiltration. #11	23 y/o male	epigastric burning pain	2.5 cm
1968	Leand et al: Obstructing esophageal polyp with eosinophilic infiltration.	36 y/o male	regurgitation dysphagia	3.5 cm
1975	Livolsi et al: Inflammatory pseudotumors of esophagus.	45 y/o female	UGI bleed	1 cm
		67 y/o male	dysphagia	2 cm
		65 y/o male	dysphagia	5 cm
		55 y/o female	dysphagia	2.5 cm
1978	Bleshman et al: Inflammatory esophago-gastric polyp and fold.	8 males] 20-68 1 female] yrs	heartburn	.8–2 cm
1979	Suen et al: Spectrum of eosinophilic infiltration of GI tract and its relationship to other disorders of angiitis and granulomatosis.	72 y/o male	dysphagia melena	5 cm
1979	Jones et al: Inflammatory esophagogastric polyp in children.	15 y/o female	abdominal pain	.7 cm
		10 y/o male	abdominal pain	.7 cm

Summary

The inflammatory esophagogastric polyp is a rare, benign submucosal lesion of the distal esophagus that may be produced as a reaction to gastroesophageal reflux. Indeed, many of these lesions are associated with the presence of a hiatus hernia and reflux esophagitis and, often, present intraluminally within the hiatus hernia. On the other hand, this mass may be a localized manifestation of a systemic process (eosinophilic gastroenteritis without blood esosinophilia) in which other areas of the gastrointestinal tract can be involved. Although, the clinical presentation may be suggestive of an esophageal lesion, it is the roentgen appearance and characteristic location of this lesion that provides for a definitive diagnosis in most cases.

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Annular Lipoma of the Mesentery as an Unusual Cause of Small Bowel Obstruction

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Lipomas of the small bowel mesentery causing intestinal obstruction are rare (1–5). In a review of the literature, only thirty cases have been documented and these case reports refer to obstruction secondary to displacement by large tumors. This report documents a case of intestinal obstruction caused by a small constricting annular lipoma of the small bowel mesentery and is presented because of its rarity.

Case Report

A fifty-three-year-old white female was admitted for crampy abdominal pain and vomiting. The pain began four days prior to admission in the lower abdomen and was not relieved by vomiting on the subsequent day. The abdomen began to distend and the patient entered the hospital. The patient had an appendectomy 30 years prior to admission. On admission, the abdomen was distended with hypoactive bowel sounds. There was a healed McBurney incision in the right lower quadrant with mild tenderness in that area with rebound. Radiographic studies of the abdomen showed distended loops of small bowel with air fluid levels and no gas in the colon. A nasogastric tube evacuated 2000 cc of bile stained fluid. The patient was taken to the operating room with a diagnosis of intestinal obstruction and at laparotomy, a mesenteric lipoma was found to be encircling the small bowel, approximately 75 cm from the ileocecal valve. The lipoma measured 9 × 3 × 2 cm and originated from the small bowel mesentery and extended on either side of the bowel in an annular configuration causing complete obstruction (Fig. 1). The proximal distended bowel was immediately decompressed after blunt separation of the lipoma. One limb of the lipoma was reduced to the opposite side of the mesentery through an existing defect (Fig. 2). The lipoma was then excised and the mesenteric defect closed with absorbable suture. The patient made an uneventful recovery.

Discussion

Fatty tumors may arise from the mesentery itself or they may be the result of a spreading out of fatty tissue from the retroperitoneum, especially perirenal fat (1). These tumors are usually diagnosed on upper gastrointestinal series by displacement of the bowel or at laparotomy (2). As the lipoma grows in the mesentery, the section of bowel adjacent to the mesentery becomes draped around the periphery of the tumor. As the mass enlarges, this section of bowel is stretched and may give rise to obstructive symptoms (3).

A small annular lipoma of the mesentery giving rise to intestinal obstruction has not been reported previously. The tumor, which was dumbbell in shape, adhered to its counterpart and likely caused a small inflammatory reaction which constricted the bowel and gave rise to intestinal obstruction.

When encountered at operation, mesenteric lipomas should be removed because when they reach considerable size, they may cause obstructive symptoms or rarely degenerate to become sarcomas (1).

Summary

Lipomas of the small bowel mesentery are rare and may give rise to obstructive symptoms when

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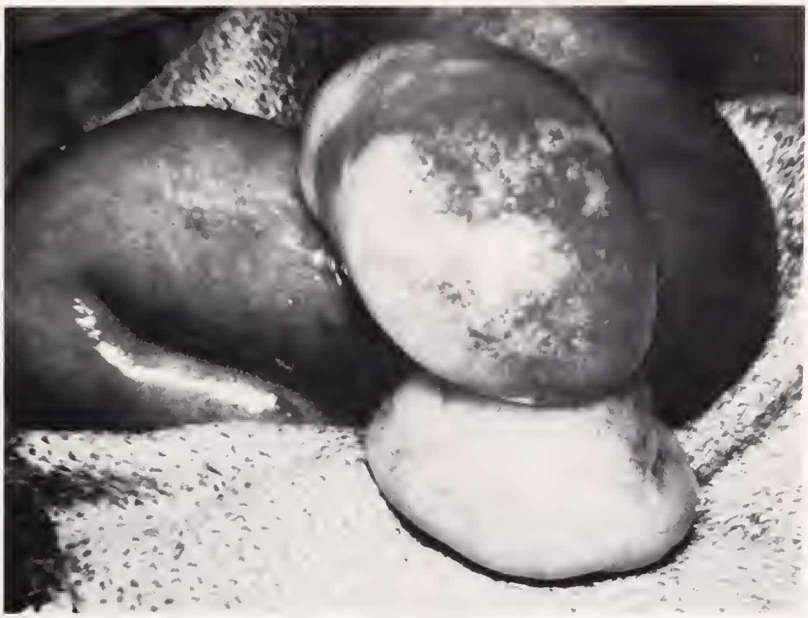

FIG. 1. Lipoma of small bowel mesentery. Note proximally dilated small bowel at right.

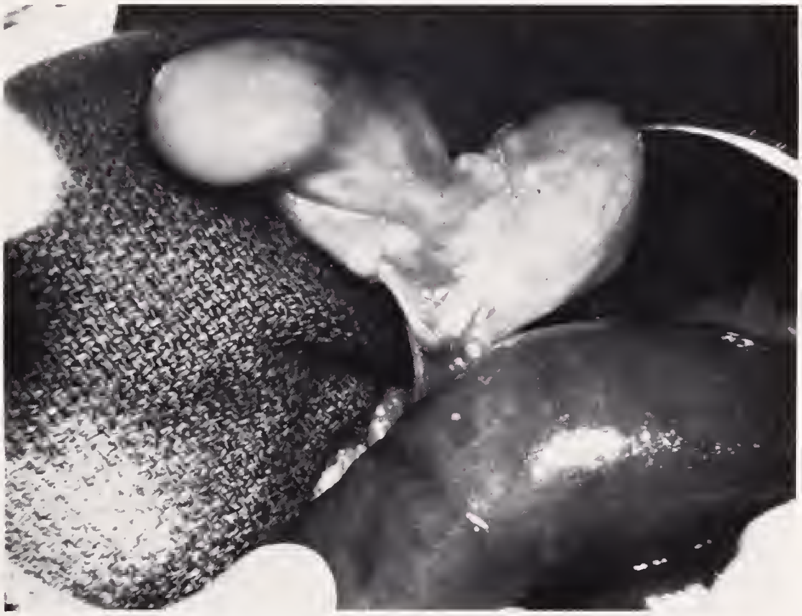

FIG. 2. One limb of lipoma reduced through mesentery. Note common pedicle.

large or by annular constriction. When incidentally encountered at operation, they should be removed.

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Prevention of Ischemic Acute Tubular Necrosis with Tris Buffer or Prostacyclin Infusion

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Introduction

One of the major problems of cadaveric kidney transplantation is damage produced by ischemia during kidney retrieval which is clinically manifested as acute tubular necrosis (ATN). It is essential to find adequate modes of protection from this damage. Methods currently used attempt to alleviate the ischemia by: providing increased flow to the kidney, delivering more oxygen, preventing vasoconstriction, decreasing cellular swelling, and inhibiting accumulated toxic metabolites (1).

The exact etiology of ATN is unknown. There are suggestions that the basic lesion may be the result of thrombocytic aggregations in the renal microcirculation and/or capillary stenosis as a consequence of endothelial and tubular epithelial swelling due to ischemia (2, 7, 9).

Prostacyclin (PGI_2) is a prostaglandin that has been shown to be a potent vasodilator and platelet deaggregator in experimental animals as well as in human subjects (3, 6). Like all prostaglandins, PGI_2 is derived from arachidonic acid, a 20 carbon, unsaturated fatty acid. PGI_2 is the product of a specific enzymatic conversion of the parent arachidonic acid. The pharmacologic manifestations of PGI_2 occur very rapidly. Under certain physiologic conditions, PGI_2 converts rapidly to $PGF_{1\alpha}$ (8), a stable but much less potent prostaglandin (3). It is postulated that platelet deaggregation results from an increase in cyclic AMP due to adenyl cyclase stimulation by PGI_2 (3) and that the profound vasodilatation is modulated by its action on the renin release mechanism of the kidney (4, 6) or direct interaction with vessel endothelium (5). These attributes of prostacyclin suggested it might be useful in the prevention of ATN.

Materials and Methods

Male Sprague-Dawley rats, weighing approximately 250g were divided into groups of five about one week after their receipt in the animal facility. They were fed rat chow and water ad lib. Base-line blood urea nitrogens (BUN) were obtained on all animals from blood collected from the tail. All BUN's were determined in a Beckman BUN analyzer on serum. Proper controls and dilutions when indicated were included. PGI_2 was prepared in a Tris buffer at pH9 every 48 hours and kept at zero degrees centigrade.

Animals were anesthetized with ethyl ether; the abdomen was shaved, the area prepped with ethanol and the animals placed in a restraining holder. A midline incision was made 2 cm below the xyphoid process to above the pubis. The peritoneal contents were reflected to expose the right kidney. The renal capsule was removed by microsurgical technique, the renal vessels ligated and cut and the kidney removed. Next, the left kidney was exposed and the renal artery and vein isolated. Silk (6-0) was placed around each vessel in loop formation in preparation for occlusion and in a location which prevented collateral circulation.

To produce acute tubular necrosis, both vessels were ligated by closing the looped silk sutures. All injections were performed with a 30 gauge steel hypodermic needle directly into the renal artery and with a volume of 1 ml. During the period of occlusion, the peritoneal contents and the kidney were kept moist with saline (0.9%

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NaCl) soaks containing penicillin. At the termination of the occlusion period, ligatures were released and the body cavity closed. The animals were placed under a heat lamp for a ten-minute recovery period and returned to metabolic cages. Daily urea nitrogen levels and 24-hour urine volumes were determined for one week, postoperatively. To establish optimal occlusion times, groups of animals were tested at varying time periods of acute ischemia. Ninety minutes proved to be optimal for the production of reversible acute tubular necrosis as measured by urea nitrogen increases and survival of the test objects.

Seven groups of rats were used. *Group 1* was occluded for 90 minutes without injection; *Group 2* received a 1 ml injection of buffer at the start of the ischemic period; *Group 3* was injected with PGI$_2$ (.15mcg/Kg) at the start of occlusion; *Group 4* was injected with PGI$_2$ (1mcg/Kg) also at the beginning of occlusion; *Group 5* was injected with buffer at the end of the 90-minute occlusion; *Group 6* was injected at the end of the ischemic period with .15mcg PGI$_2$; and *Group 7* was injected with 1mcg/Kg PGI$_2$ at the end of the ischemic time.

Injections at the start of the ischemia time were done immediately following occlusion of the renal artery. After injection, the renal vein was also occluded. Injections at the end of the ischemic period were given as soon as the renal vein ligature was released, with subsequent arterial release post injection. Those animals receiving PGI$_2$ at the end of the occlusion, required 15 minutes of direct but nonocclusive pressure to prevent hemorrhage.

Statistical analyses were done with the students' t test.

Results

The majority of rats were polyuric; however, some presented with anuria and oliguria. Therefore, renal function was measured by BUN serum levels (Fig. 1–2, Table I). In the control group, the mean of the urea nitrogens rose from 62 to 140mg% in 24 hours and peaked at 48 hours at 170mg%. The urea nitrogen values remained elevated during the five postoperative days but displayed a slow, yet steady decline toward the base-line values. By the end of the seven-day period, many had returned to the range of base-line BUN's. The group receiving buffer at the time of occlusion did not display a statistically significant rise in urea nitrogens. As Figure 1 depicts, these animals showed slight increases in BUN at best which returned to low values by the third post-

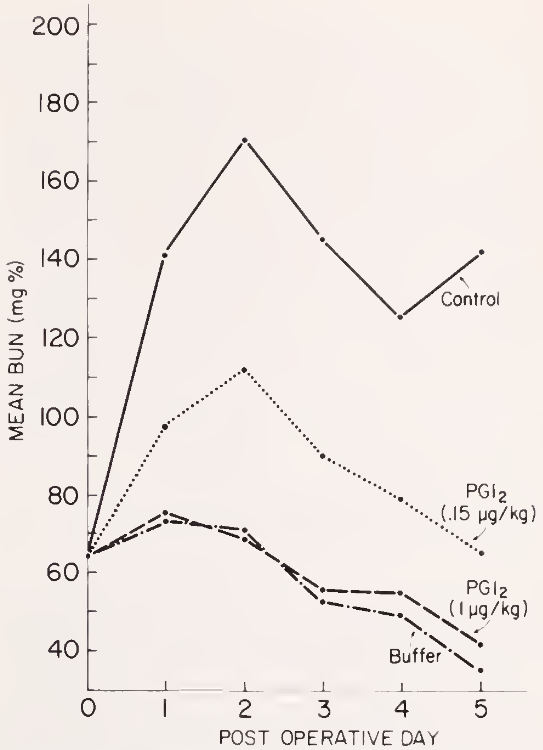

FIG. 1. Pre-ischemic injection. This graph depicts significant protection from ATN using buffer and high dose PGI$_2$ with respect to control.

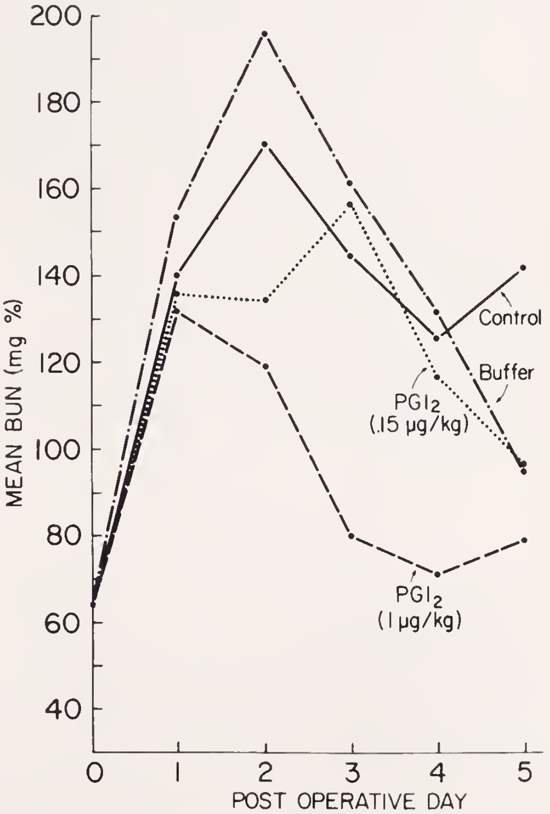

FIG. 2. Post-ischemic injection. This graph shows the failure of buffer or PGI$_2$ (high or low dose) to prevent a rise in BUN similar to the control group.

TABLE I
Bun Values

Group	N	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Control	8	87 ± 44	140 ± 34	170 ± 113	144 ± 97	131 ± 104	141 ± 143
Buffer BO	5	61 ± 14	73 ± 20+	71 ± 32*	53 ± 20*	49 ± 18	35 ± 10
PGI_2 .15mcg/Kg BO	5	40 ± 16	97 ± 46	112 ± 68	90 ± 54	79 ± 39	65 ± 28*
PGI_2 1mcg/Kg BO	3	57 ± 22	75 ± 13*	69 ± 29*	56 ± 19*	55 ± 5	42 ± 21
Buffer AO	6	45 ± 16	154 ± 42	195 ± 117	161 ± 81	131 ± 19	95 ± 58
PGI_2 .15mcg/Kg AO	6	59 ± 28	136 ± 34	134 ± 42	156 ± 101	116 ± 101	95 ± 91
PGI_2 1mcg/Kg AO	4	87 ± 27	132 ± 22	119 ± 53	80 ± 34	71 ± 19	78 ± 23

BO = Before occlusion
AO = After occlusion
* = p value <.05 as compared with control
+ = p value <.001 as compared with control

operative day. At no time was any urea nitrogen value in this group of animals significantly different than controls. The low-dose PGI_2 injected at the start of the occlusion resulted in urea nitrogen elevations intermediate between ATN and baseline values. Thus, after 24 hours the mean BUN of this group was 97mg% which peaked at 112mg% in 48 hours but returned to base-line values by the fifth postoperative day. Therefore, low dose PGI_2 eliminated the effect of buffer. The high dose of PGI_2 administered at the start of the occlusion resulted in urea nitrogen levels comparable to the results obtained with buffer administered at the time of occlusion as demonstrated in Figure 1. Entirely different results were obtained when we delayed injections to the end of the ischemic period (Fig. 2). No difference between the acute tubular necrosis control group and the variously treated groups was evident 24 hours postoperatively. In general, the postocclusion treatment may have modified acute tubular necrosis slightly, especially the PGI_2 high dose regimen, but at no time did these differences become statistically significant.

Discussion

Our results with Tris Buffer pre-ischemic treatment, introduced merely as a control, showed protection from ATN that is in accordance with previous publications. A very elegant investigation by Summers and Jamison (2) addressed the role of saline in the prevention of ATN. Using heparinized rats with a 60-minute ischemic period, these investigators studied renal blood flow by carbon particle infusion and renal function by the glomerular filtration rate.

Their surgical approach differed from the one used in our experiment. To occlude renal blood flow, they clamped the renal pedicle but perfused the kidney with saline for ten minutes prior to occlusion by ligating the aorta to institute flushing and the vena cava to prevent congestive heart failure. Their results indicated that saline modified the reflow phenomenon considerably but did not prevent endothelial and tubular epithelial edema as demonstrated by ease of carbon particle passage, but impaired ability to tolerate red cells or their ghosts in the renal microcirculation. This modifying effect of saline on kidney injury resembles our results. In our experiment, the 1.0ml single flush of the kidney prevented the overt manifestation of acute tubular necrosis as measured by BUN.

The similarity of response to both buffer and high-dose PGI_2 suggests that further studies are necessary to establish the relationship, if any, between the mechanical displacement of blood by buffer and the beneficial effects other than mechanical displacement which may result from high-dose PGI_2. The inhibition of the buffer protective effect by the addition of a low dose of PGI_2, when injected at the time of ischemic onset, allow us to speculate that this drug in low dose might exert an as yet unexplained pharmacologic effect in opposition to its known activity.

All groups in which ATN was produced returned to baseline BUN values by the seventh postoperative day. However, pre-ischemic treatment with buffer or PGI_2 in high doses prevented any rise in BUN. Our findings would suggest that it is advisable to flush donor kidneys with buffer as soon as possible after their removal. Further studies are necessary to show that the addition of adequate doses of PGI_2 may enhance the benefits of buffer in the preservation of these organs.

Summary

Acute tubular necrosis (ATN) was produced in seven groups of Sprague-Dawley rats by occlusion of the left renal vessels for 90 minutes after right nephrectomy. Renal function was determined daily for one week by measurements of blood urea nitrogen (BUN). Injection of Tris Buffer at the time of occlusion significantly decreased the severity of ATN. Low dose of prostacyclin (PGI_2) (.15 mcg/Kg in 1 ml buffer) injected at the time of induction of ischemia suppressed the beneficial effect of buffer injection. A higher dose of PGI_2 (1 mcg/Kg in 1 ml of buffer) administered at the time of occlusion showed similar effect to the one obtained with buffer alone. Post-ischemic administration of these agents did not show any protective effect. It is concluded that the perfusion of the kidney with buffer before occlusion as well as the injection at the same time of PGI_2 1mcg/Kg produce a protection against the ischemic damage. To clarify the role of PGI_2 in this protective effect, further experiments are necessary.

Acknowledgments

The authors would like to express appreciation to the Upjohn Company, Kalamazoo, Michigan, for supplying the prostacyclin used in this work.

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Pyopneumothorax as a Complication of Pseudomonas Aeruginosa Bronchopneumonia: A Case Report

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Spontaneous pyopneumothorax as a complication of Pseudomonas aeruginosa bronchopneumonia is rare. We had the opportunity to study such a patient. We report the case and discuss possible contributing factors.

Case Report

A 41-year-old man was admitted for evaluation of fever, jaundice and a 35 lb weight loss during the preceding month.

Myasthenia gravis was diagnosed in 1969, eleven years prior to death. A thymectomy was performed in 1970. The thymus showed follicular hyperplasia, and there was no improvement following surgery. Respiratory difficulties necessitated permanent tracheostomy in 1976. Plasmapheresis was started one year prior to death, and improvement followed. The patient's medical treatment included: physostigmine, corticosteroids, and azathioprine, which was discontinued when he became jaundiced.

The patient was in mild respiratory distress when admitted, with a respiratory rate of 30/min. Temperature was 101.2°F, and the pulse rate was 130/min. The permanent tracheostomy tube was in place. Scleral icterus was noted. Muscle weakness, especially in the neck and shoulders, was demonstrable. Chest x-ray documented a right middle lobe infiltrate. The glutamic oxaloacetic transaminase determination was 287 mU/ml and the bilirubin was 7.9 mg/100 ml. The white blood cell count was 9,500/mm^3 with a left shift. Other laboratory studies, including serologic studies for hepatitis viruses, were unremarkable.

The patient's breathing was assisted by a ventilator. Despite massive antibiotic treatment, he developed severe respiratory distress, possibly following an episode of aspiration. Extensive bilateral bronchopneumonia, with multiple bilateral abscess formation was seen on chest x-ray (Fig. 1). Bacteriologic culture of lung tissue, obtained from the middle lobe via transbronchial fiberoptic bronchoscopy, grew Pseudomonas aeruginosa. He developed left-sided tension pneumothorax (Fig. 2), and expired on the eighth hospital day.

Postmortem Examination

Major autopsy findings were in the respiratory system. The left pleural cavity contained 2000 ml of air, and there was also mediastinal and subcutaneous emphysema. Both pleural cavities contained fluid. The right pleural cavity contained 100 ml of clear, bright yellow, watery fluid, and in the left hemithorax there was 450 ml of thick, grey-yellow fluid, which had a slightly reddish hue.

The lungs weighed 2500 grams together, and were diffusely consolidated and poorly aerated. The cut surfaces of both lungs were firm and granular, and many of the bronchi were filled with mucous secretions. Microscopically, there was a confluent bronchopneumonia with multiple microabscesses and areas of organization. Each lung contained two, 3–4 cm large abscesses filled with pus. The pleural surface of the lingular abscess was ruptured (Figs. 3, 4). Pseudomonas aeruginosa and Serratia marcescens were cultured from both lungs and the left pleural cavity, and Pseudomonas aeruginosa was cultured from the spleen.

The liver was markedly enlarged, weighed

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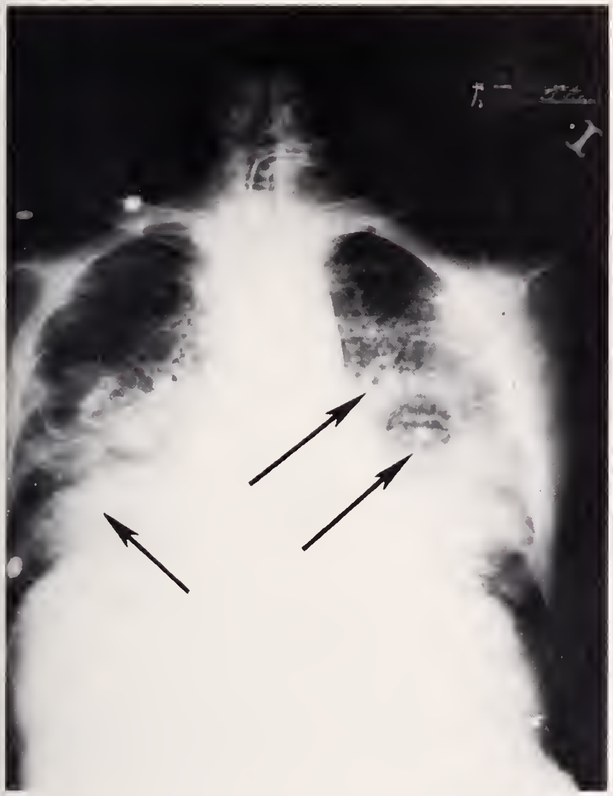

FIG. 1. X-ray showing extensive bilateral bronchopneumonia with multiple abscess formation in both lungs. Arrows point at abscesses.

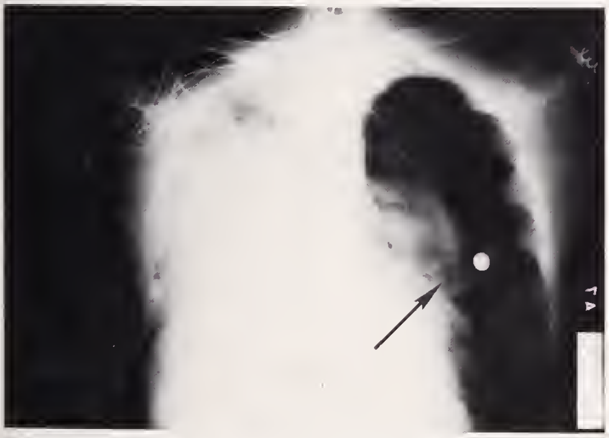

FIG. 2. X-ray showing left sided pneumothorax and left lung atelectasis. Arrow points at lingular abscess.

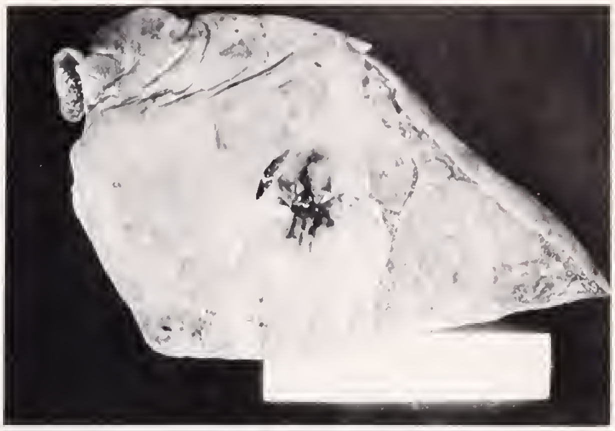

FIG. 3. Pleural surface of ruptured lingular abscess.

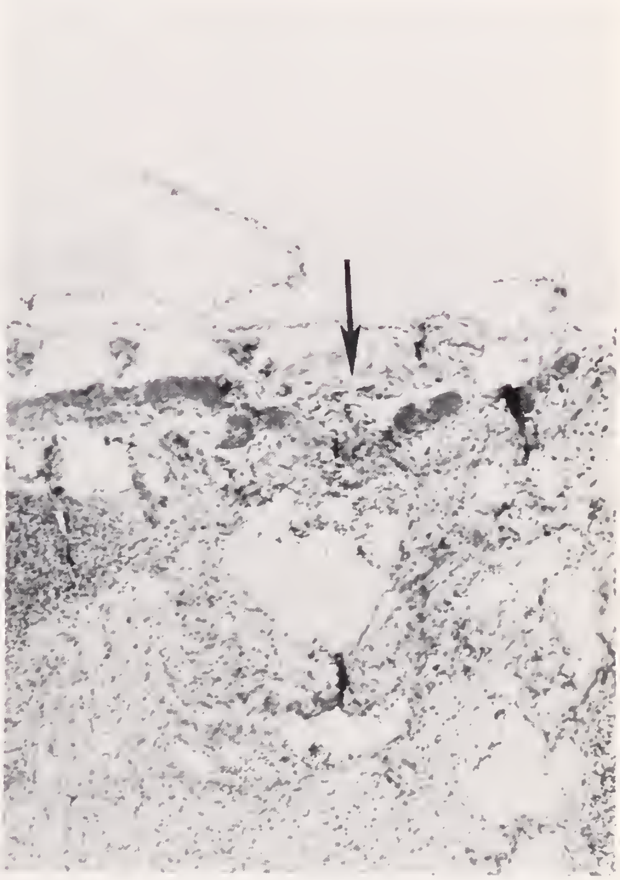

FIG. 4. Photomicrograph (hematoxylin-eosin stain, original magnification ×40) of the pleural rupture site. Arrow points at the rupture site.

2870 grams, and was covered by a tense hepatic capsule. Histologically, however, there was no hepatocellular necrosis. Cholestasis was prominent, and the portal tracts showed a mild inflammatory cell infiltrate with bile duct proliferation and slight fibrosis.

Discussion

Spontaneous pneumothorax that occurs as the result of a clinically manifest disease is categorized as secondary spontaneous pneumothorax. Spontaneous pneumothorax secondary to bacterial pneumonia results from pleural disruption in an area of necrosis or abscess formation (1). Putrefactive lung abscess secondary to aspiration pneumonia is an important cause of pyopneumothorax in the adult (1, 2).

Pyopneumothorax complicating Pseudomonas aeruginosa pneumonia is rare, and was not mentioned in any of the patients described in two large series of Pseudomonas aeruginosa infection (3, 4).

Factors predisposing to abscess and pyopneumothorax formation in Pseudomonas aeruginosa pneumonia in our case included chronic debilitation and hospitalization, immunosuppression with steroids and azathioprine, prior broad spectrum antibiotic treatment, as well as breach of normal mechanical barriers in the upper airway by tracheostomy and continuous ventilatory support (2, 4–7). Pseudomonas aeruginosa pneumonia in patients with these predisposing factors has poor prognosis (2). Pyopneumothorax can contribute to a dramatic worsening of a patient's condition, with development of severe dyspnoea and cyanosis (1), and mortality may be as high as 80%. Symptoms may be masked by steroid therapy (8, 9). Early diagnosis and drainage of the pleural cavity is mandatory (9, 10).

Cholestatic hepatitis has been associated with azathioprine therapy (11). We cannot, however, definitely exclude the possibility of non-A, non-B hepatitis, which may manifest as cholestasis with a predominantly portal infiltrate (12).

Plasmapheresis is used in the treatment of myasthenia gravis in order to eliminate autoantibodies, which react with the acetylcholine receptors of the skeletal muscles (13).

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The Santorini Valves

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Giovanni Domenico Santorini was born in Venice, Italy, in 1681, and proved to be one of the most accomplished anatomists of the Italian school of medicine. When only 22-years old, the Physico-Medical College of Venice appointed him Public Professor of Anatomy. According to one of his biographers, his lectures were so successful that their brilliancy persisted until his death in 1737.

In 1724, he published his *Observationum Anatomicarum* in Venice. Subsequently and until his death, he worked on another book which was never published. However, he left a whole collection of illustrations with the corresponding descriptions. All this material was compiled and published by his disciple Michael Girardi in Parma, Italy, in 1773, under the heading of *Anatomici Summi-Septemdecim Tabulae* (Fig. 1).

Girardi was Primary Professor of Anatomy of Parma University and was the favorite disciple of Santorini who had left very complete notes describing each illustration. Girardi added numerous explanatory notes with scrupulous regard for Santorini's original descriptions.

Although the object of this paper is to discuss the valves discovered by Santorini, I believe it is very important to transcribe the more detailed descriptions he gave of the entire terminal portion of the biliary and pancreatic ducts, the caruncula major, and the duodenal mucosa.

According to Girardi, Santorini personally undertook several hundred duodenopancreatic dissections which he studied minutely with the aid of a magnifying glass. All his illustrations were drawn to scale, thus enabling the true size of the structures to be appreciated. (Fig. 2).

With regard to the importance of Santorini's discoveries, we have deemed it important to comment upon paragraphs VII and VIII of his book *Observationum Anatomicarum,* and illustrations XI, XII and XIII, with which he afforded proof of his discoveries.

In paragraph VII Santorini dealt with "the position and relation of the duodenum," in the following terms:

> "And it is necessary to add something so far scarcely noticed which it is advisable not to omit, regarding the so-called duodenum. I refer both to its location and to some of the things it contains.
>
> "Everyone knows that the duodenum is a continuation of the pyloric opening. Now, however, that it is mounted two or three finger-widths above the same pylorus, although it has always been admitted, it is not accepted by renowned anatomists. Moreover, that with its tortuous course with a slight inclination it introduces itself between the gallbladder and the pancreas; thence, advancing somewhat transversally above the vena cava and beneath the portal vein, it ascends again with another fold, its parts being firmly united and tied everywhere until it becomes impossible to remove it from that position, it becomes lodged under the ventriculus where, with a right-angle fold, it turns downwards; however, being then loosely united to the mesenterium it turns towards the jejunum, this being the terminus of the duodenum, which apparently should be constituted both on account of its flux and firm connections, more appropriately than on account of its twelve fingers' measure."

Santorini then attempted an explanation of this special anatomic configuration of the duodenum. In his opinion, the reason thereof was that the "less elaborated" contents of the stomach should not be emptied too rapidly into the intestines.

". . . which should be the object of admiration inasmuch as Nature has directed thereto the two humors from the liver and the pancreas, through

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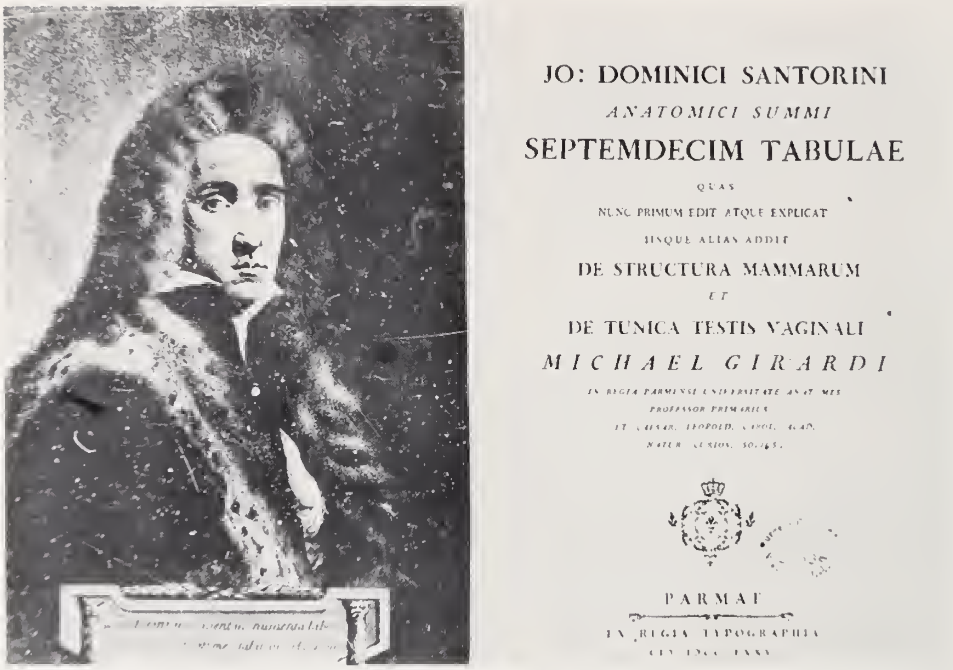

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ANATOMICI SUMMI
SEPTEMDECIM TABULAE
QUAS
NUNC PRIMUM EDIT ATQUE EXPLICAT
IISQUE ALIAS ADDIT
DE STRUCTURA MAMMARUM
ET
DE TUNICA TESTIS VAGINALI
MICHAEL GIRARDI
IN REGIA PARMENSI UNIVERSITATE ANAT. MED.
PROFESSOR PRIMARIUS
ET CAESAR. LEOPOLD. CAROL. ACAD.
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PARMAE
IN REGIA TYPOGRAPHIA
CIƆ IƆCC LXXV

Fig. 1. JO: DOMINICI SANTORINI. Introduction to *Anatomici Summi Septemdecim Tabulae.* Parma, 1575.

whose action final perfection takes place there of what was not accomplished in the ventriculus.

"It is also for this reason that the duodenum is fixed to the posterior wall, to prevent violent contractions and in order that the euchemical particles of the foodstuffs could be elaborated longer and more comfortably, nature provided narrower folds on both sides."

Santorini goes on to admonish clinicians benignly, who are advised "to direct the mind at times to those places and ponder with some care that which refers to position and relation of this intestine besides what can be thought about such numerous structures related to this gallbladder; about the superposed portal vein; about the inferior vena cava; about its greater amplitude; about the different humors meeting therein; about the retarded and dissolved food remnants between both folds. Or, on the contrary, without any regard for the nerves, vessels and viscera, should everything that takes place there be attributed always to *flatus,* as vulgarly stated, and

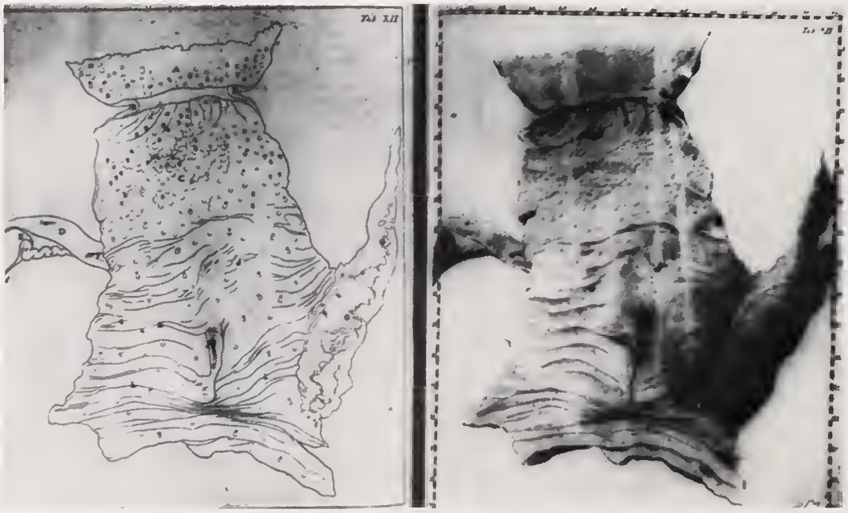

Fig. 2. Tabulae XII. Each of Santorini's figures was drawn to scale, with a detailed scheme of the different structures.

the majority of times, to *hypochondriasis*, which, to tell the truth, they only know by name everything taking place in those places."

In paragraph VIII, Santorini described everything that he found within the duodenum. Commencing with the pylorus, he minutely described the characteristics of the duodenal mucosa and how it differed from the rest of the small intestine. He drew attention to the "numberless glands of the illustrious Brunner," the absence of folds, and the "winking" (connivent) valves, in accordance with Kerckring's denomination based on their function as observed in the first portion of the duodenum. Santorini then explained that this special configuration of the first duodenal portion has, as main objective, "to facilitate the ascent of everything that flows, seeing that further down, these valves are found closely crowded and remarkably prominent."

Santorini continued with a careful description of the characteristics of the duodenal mucosa throughout this first portion, and went on to enquire:

"What is the explanation of this admirable configuration? Is it to retain something which must be mixed with the foodstuffs elaborated in the ventriculus and which arise from the pylorus; or, in order that upon completion of the transportation of the foodstuffs, the intestinal wall should not dry up, consequent upon the extraction of the humor originated therefrom or, perhaps, for some other more important and occult function? All of this is something I dare not determine."

Thereafter Santorini described, of the second portion of the duodenum, the common outlet of the secretory ducts "of twin viscera such as the liver and the pancreas, which spills into the duodenum through a single and common aperture, the transported humors. The most expert anatomists are aware, since long ago, of the fact that this aperture stands out at times, and in others it is surrounded by some form of subtle circle. Now, that it is held by a strong frenum or tie, more apparent and occasionally longer than a thumb, is something I never heard commented upon by any dissector, if my memory does not fail me".

"Such aperture extends along the intestine, where this becomes united with the mesenterium, i.e: where the previously mentioned canals open into the cavity of the same intestine. Then, slightly diminished in size, it turns downwards through the spaces of the winking valves which therein become interrupted, this being the main reason for its discovery."

This structure was named "frenulum" by Santorini and, according to his interpretation, this part of the organism which was present in almost all his observations, together with the "winking valves," is to prevent the reflux of the intestinal contents into the biliary tract by closing and obstructing the outlet of the bile and the pancreatic juice.

In Plate XI of Santorini's book the liver appears "in an inverted and lifted position in order to present its obtuse face, and to show the gallbladder and the natural site of the ventriculus and the pancreas."

This plate describes in great detail all the structures that secure the liver, the irregularities of its convex face, the hilus, the component vessels and ducts, the different hepatic lobes and their connections, the fossa vesicae. A detailed study is made of the configuration of the cystic duct and its different presentations, as well as of its internal constitution, in relation to the valves described by Ruysch and designed by Heister.

Like Vater and other contemporary authors, Santorini studied very carefully the differences in caliber both of the cystic duct, from the "gallbladder meatus" up to the union of the hepatocystic duct with the common bile duct in all its length. He emphasized its terminal bottleneck and the variations in its oblique course, all of which represent obstacles that prevent bile from flowing freely and in sufficient quantity. After a careful analysis of all the possibilities in relation to duct lumina and duct directions, Santorini added the following comment:

> "Thus, the quantity of bile must be measured, not by the amplitude of certain section of its course, but by the size, the obliquity and the pressure along its course, as well as by the narrowness of the outlet. We have stated all the foregoing not with the object of mentioning the name of the immortal author, nor of levelling charges against some occasionally napping Homero, but in order that sometime be finally understood the course of the bile and its degree of obstruction."

In regard to the terminal portion, Santorini states:

> "I believe, however, that I must point to some other things, some of which are of a constant nature, and refer to the extreme end of the canal referred to; others are met with more frequently and refer to the common bile duct."

Santorini contradicted the general opinion of his time that the common bile duct (choledochus) is larger than the ducts whole confluence leads to its formation. Instead, he upheld the opinion that it is narrower.

> "Inasmuch as I have been able to ascertain this narrowness on numerous occasions, I decided to investigate with greater attention and after drying these ducts by insufflating air, I measured them with extreme care and was able to demonstrate my point. Still more frequently in totally whole cadavers I had found such common bile ducts which evidently were surpassed, as regards amplitude, by the hepatic duct. Moreover, that this same common bile duct, the more it approaches the duodenum the more contracted it becomes, so much so that in the vicinity of the duodenum it clearly becomes funnel-shaped."

In an explanatory note, Santorini refered to the existence of the common bile duct which was accepted "by the most illustrious." As regards Santorini retained some samples of the narrowing in the terminal portion, proof of his observations and to show them to his disciples. The role of this narrowing would appear to be the result of two causes:

> "In order that the hepatic bile, rejected by the narrowings of the common bile duct, should penetrate the cystic duct, where otherwise it would not penetrate so easily. Afterwards, in order that the hepatocystic bile should not reach the duodenum in inconvenient amount as if in a torrent from a wide channel, but instead in a smooth and convenient descent."

Santorini then presented a long and detailed description of the dissections carried out both in normal and pathologic gallbladders, some of which were filled with stones. He describes the characteristics of the gallbladder mucosa and gave a long description of the fibers which follow various directions (straight, oblique and transverse) and which form part of the muscular layer of the gallbladder. Sensible comparisons are made with the urinary bladder, upholding the view that

> "The transverse cords serve to fasten, the straight ones, however, to contract. Now, if all this seems somewhat subtle and difficult to someone, and its judged that neither the structure of the gallbladder is purposeful, nor the configuration of the channels apt for the excitation and removal of such humor; in so far as I am concerned, all well and good to such dissenters. Truly I affirm only that which a long and attentively studied Anatomy teaches me. And if, in consequence of my work I hope to obtain something through its intermediary, by the same token I believe in that which sane reason teaches me, that is: that it has never been demonstrated that the Creator's designs have proved in vain, that His work is everlasting."
>
> "However, allow me to add this lest it be believed that I have affirmed these things inconsiderately, that is: That, in those whom death snatched suddenly and rapidly through disease of the entrails or through suffocation, I always found an empty gallbladder which I believe was not discharged by respiratory problems but as a result of violent commotion of each of the parts, and through nerve distention."

The same illustration also shows the stomach, then known as the "ventriculus," the esophagus, the pancreas and an open duodenum with the orifices corresponding to the two caruncles. It is worth pointing out that, in his description, Santorini makes a careful identification of the muscular layers of the stomach and the esophagus. Furthermore, he remarks upon the existence of perihepatic lymph nodes, and points to the possibility of serious disease as a result of pathologic changes.

Plate XII deals with "the duodenum and in it are mainly shown: the outlet, the site, form and number of ducts pertaining to the liver, the gallbladder and the pancreas, the beginning and arrangement of the folds."

As stated, this plate mainly depicts the duodenum from the pylorus up to the third portion overpassing the outlet of the choledochus and Wirsung's duct. It is remarkable how elaborately he describes all the irregularities and characteristics of this area. Moreover, to establish the pertinent relations, the plate also shows part of the cystic and hepatic ducts, the choledochus, and the head of the pancreas. After describing the glands of "the illustrious Brunner" and the differences in the aspect of the mucosa from the pylorus to the jejunum, the two caruncles are described as follows:

> "At 'f' can be seen and almost conical-shaped caruncle at the extremity of whose

vertex lies the small opening of the upper pancreatic duct, through which we have met with no difficulty in introducing either a bristle or a stylet.

"At 'h' is shown the greater caruncle at whose center 'g' there is an oblong opening visible constituting the peculiar aperture of the common duct proceeding from the liver and the gallbladder, as well as from the main pancreatic duct. This caruncle which is as long as the width of a thumb, is located at the left of the duodenum, and depending upon its length may show a slight curve at its arch, adjusted to the smooth curvature of the duodenum, conspicuously standing out for the most part, advancing in the midst of the intestinal membranes with a delicate protuberance almost like a quill, and presenting at its base an aspect somewhat similar to that of a slightly curved cylinder, whose lower and diminished portion, cut almost obliquely, prolongs itself with an evident restraint, as thick as a thumb length, which diminishes insensibly and becomes even with the internal membrane of the intestine. However, the upper part of this caruncle is covered by a fold or valve, which I never noted descended to such an extent as to totally close its opening. This fold, or the first or undoubtedly one of the first, present in the duodenum, below the pylorus. In regard to this valve the illustrious Prosector Morgagni expresses: 'At the opening of this main caruncle and along all the protuberance of the cylinder I saw, both before and recently in six open cadavers, a superposed valve so evident that I am surprised at its omission by some, and, more so, its denial by others'."

In his comments regarding these valves, Girardi transcribes the following statement by Morgagni:

"So far to my knowledge no one has described these valves, with the exception of the most illustrious and beloved Giovanni Domenico Santorini, King's Physician at Venice and at present Professor of Anatomy, who gave his name to the frenulum or ligament of this opening."

Santorini then adds:

"However, as regards the form and size of the frenulum, although I often established variations between them in keeping with the diversity of the bodies, only on very rare occasions, in hundreds of observations, do I recollect its absence. I do truly remember its elegant shape occasionally divided into two parts before the opening; I also remember having found a tripartite division. I realized that this division took place when, either from the sides of the tripartite division or from below in the bipartite division, the frenulum ended with the initiation of the folds or winking valves at that opening. It is likely that the frenulum was located there in order that the opening should not face entirely the opposite wall of the intestine. Moreover, I feel that the frenulum was not located uselessly nor unexpectedly; but in order that the mouth should not be round nor excessively open, permitting the easy collection at that place of the back flow of the intestinal juices. As a matter of fact, on account of this frenulum the opening, being pulled downwards and thus becoming oblong in shape, and highly acute in its lower part in order that nothing should obstruct or reject the juices endeavoring to become infiltrated from below. On the other hand, this same shape of the mouth contributes in a high degree, among other things, towards increasing its narrowness. Thus, the site of the same protuberance and of opening, located in the left bulgy side of the duodenum, constitutes a powerful impediment to the easy access of the humors returned from the intestines."

Finally, it is added: "I thus consider this opening to have diminished in amplitude not only on account of the change in its form, but as a result of its very narrowness and folds, to the point that its capacity not only does not respond to the two confluent canals, but not even to each of them; not to the narrower which is the pancreatic one, that, on account of some fat accumulated at the extremity of its walls becomes even narrower. I also found occasionally that this opening was so narrow in healthy and young subjects, that it was with difficulty that I could introduce a somewhat thick bristle, even though its inside capacity, shaped like a bladder, much exceeded that of the same opening at which confluence takes place separately of the hepatic and pancreatic ducts, which are more ample than the outlet itself. From all the foregoing it can be inferred that Nature constituted this part in such a way as to set aside the exterior humors so that they do not invade excessively; at the same time repressing and moderating the interior ones so that they do not flow superabundantly."

"However, there is something more, truly small and insignificant but greatly important, not emphasized or, in so far as I know, not pointed out or commented upon by anyone, that is: certain small valves which, located at the extreme of the canal, are found just before the opening. I have always been able to find them there, particularly, where the narrowness of the canal does not eliminate every possibility of observing them. As a matter of fact, as if that complex orifice which Nature has placed there (that is: the protuberance, the curves, the fatness, the frenulum, the shape and narrowness of the aperture, were not sufficient to fulfil the purpose, it also added some valves, truly small ones, but sufficient to accomplish their aim.

"It is usually easy to visualize them if election is made of the part of a vast cadaver (which will enable an easier vision), and it is then carefully cleaned. They are then explored by insufflating air or introducing a lancet; or removing them with clean water. The caruncle is then sectioned longitudinally with great care, and this enables a clear view of the valves.

"Of these valves one is occasionally larger than the rest. At times both are almost equal in size and the lateral union between them do not permit an easy entry inasmuch as they become enlarged with the insufflated air or through the introduction of the lancet, thus obstructing the passage. The valves are sometimes shaped like the letter "S"; on other occasions they resemble a longitudinally sectioned cone, almost similar to the vein valves. Sometimes they resemble a line in amplitude, occasionally they are larger. They are positioned in such a way that conjointly they are placed before both ducts; however, they seem to take care, preferably, of the nearer and lower aperture which corresponds to that of the pancreas.

"Besides these greater valves which I sometimes find unstable in so far as concerns shape, order and number, though highly stable as regards position, there are other minor valves located between the acute meatus and the extremity of that opening. They present a net-like arrangement facing the major valves. They fulfil the same function, which is to prevent everything from flowing therein from the intestinal cavity on account of the strong and frequent pressures of such parts and of the humors flowing between such parts. However, in case someone should object what has just been asserted, by stating that such valves are non-existent, or that they do not fulfil the functions we attribute to them, let it be known that it is possible and easy to introduce deeply into such opening the lancet or to insufflate air therein. Truly, the situation is different with respect to the introduction of the lancet or the force of the insufflated air in the case of the humors which endeavor to become infiltrated. Both the lancet and the air, once they have penetrated the first part, duly extended and prepared, can overcome easily, either the opposition of the highly delicate valves, or prevent the resistance and confrontation thereof in view of the fact that the humors (which for their part, endeavour to invade, upon pressing against the same caruncle) they themselves close the opening. And if occasionally some flowing takes place there, this must be in such a manner that it does not prevent the correct position of the valves, nor overcome the resistance of such a number of them. This was often evident to me (especially today, when I write about these things) in the lymph ducts in which the insufflated air advances without difficulty against the valves by overcoming their resistance, which probably is inconvenient to the lymph therein contained.

"Instead in my last observations I found a very ample opening of that common duct, which was confronted not only by very ample and visible valves which repressed the thrust both of the humors and of the air, as well as of the lancet; but also by an embolus. This forces one to state that Nature protects the more ample openings with the maximum defenses."

One cannot ask for a more complete and precise description of these valvular formations at the terminal portion of the common bile and Wirsung's ducts. Nearly one century before Santorini, Vesalius (1) dealt with these formations upon describing the ductus choledochus. In Chapter VII of Book V of his *De Humani Corporis Fabrica,* dealing with *The Bladder of the Yellow Bile* Vesalius refers to the common bile duct in the following terms:

"Resting upon the lower membrane of the epiploon it turns inwards, somewhat obliquely, and it settles on the duodenum, not far from the commencement of the jejunum. This branch transports the bile expelled by the gallbladder to the intestines, without admitting anything from them, neither solids nor gases, nor eventually the backflow of the same bile which it had transported. Which is due, not only to the tortuous entrance into the intestine *but also to the two membranes which, from both parts, next to the orifice, hang loosely, yielding easily to the bile flow and* *preventing any retrogression towards the duct inasmuch as once folded up within the mouth of the duct, this becomes occluded.*"

For our part, we have found these membranes on several occasions and were able to photograph them (Fig. 5).

Subsequent to Santorini's observations it was towards the middle of the 19th century that Claude Bernard (2) "refound" these membranes. In several of the illustrations of his famous *Memoire sur le Pancreas,* Bernard depicts the valves discovered by the Italian investigator.

Towards the end of the same century, Simon Gage (3) dealt with these valves and remarks upon the apparent oblivion into which they had fallen.

In 1909 Oscar Stracker (4) published a very complete and authoritative study about the main papilla which he denominated *plica longitudinalis,* and also dealt with these valves, some of their characteristics being adequately illustrated.

In 1917, Torston Rietz (5) published a lengthy article about the extrahepatic biliary tract, and illustrated two different aspects of these formations. The pertinent illustration was subsequently reproduced by O. Hulton 1938 and by P. Mirizzi in 1939 (6).

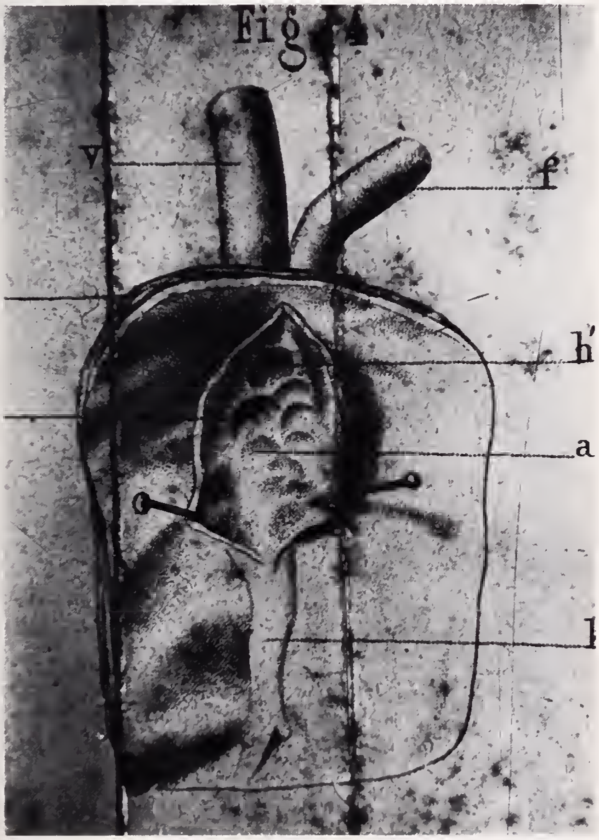

Fig. 3. The ampoule is open with Santorini Valves. Claude Bernard, *Memoire sur le Pancreás,* Fig. 4.

More recently, J. O. Brown and R. J. Echenberg (7) presented to the American Association of Anatomists, March–April 1964, a new study about the valves discovered by Santorini in 1720 and made known by Vesalius in 1543, in which the authors named described them as *mucosal reduplications.*

In seems, however, that they had not read the original descriptions by Vesalius and Santorini since they referred to what they had read in a paper by Boyden. The same applies to Claude Bernard's description, also quoted by Boyden. These "second hand" references are regrettable because otherwise they would not have concluded: "These investigators carried no further their obviously incomplete and somewhat confusing descriptions of the ampullary-related morphology; no pertinent account of this region has been given until the initial findings depicted in the preliminary report of Schenberg and Brown."

Vesalius' description of the *membranes which hang loosely* and of their probable functions are truly the earliest observations. The photographs of these valves obtained by me between 1957 and 1961 confirm Vesalius' exactness.

Regarding the descriptions by Santorini, from 1720 to 1737 (not 1775 as stated by Echenberg and Brown) it is sufficient to read the foregoing transcriptions to affirm conclusively that it was Santorini who discovered them, established their characteristics, their shape, size, position and frequency, and, what is more remarkable, assigned to them the main function of safeguarding the entry to the pancreatic duct. His illustrations, drawn to scale, are of such perfection and charm, that they have not yet been surpassed by any anatomist.

For Claude Bernard, the comments are likewise tremendously unjust since besides being a physiologist, he was an outstanding anatomist who, to complement his studies on the pancreas, carried out innumerable dissections in corpses and in many animal species. The illustrations presented by him in his famous *Memoire sur le Pancreas* furnish us with the first images of Santorini's valves.

In view of the foregoing, I consider it would be an act of justice to name these formations after their discoverer: Giovanni Domenico Santorini.

In conclusion I must add, it is somewhat more than forty years that I have been studying this area, erroneously known as the ampulla of Vater

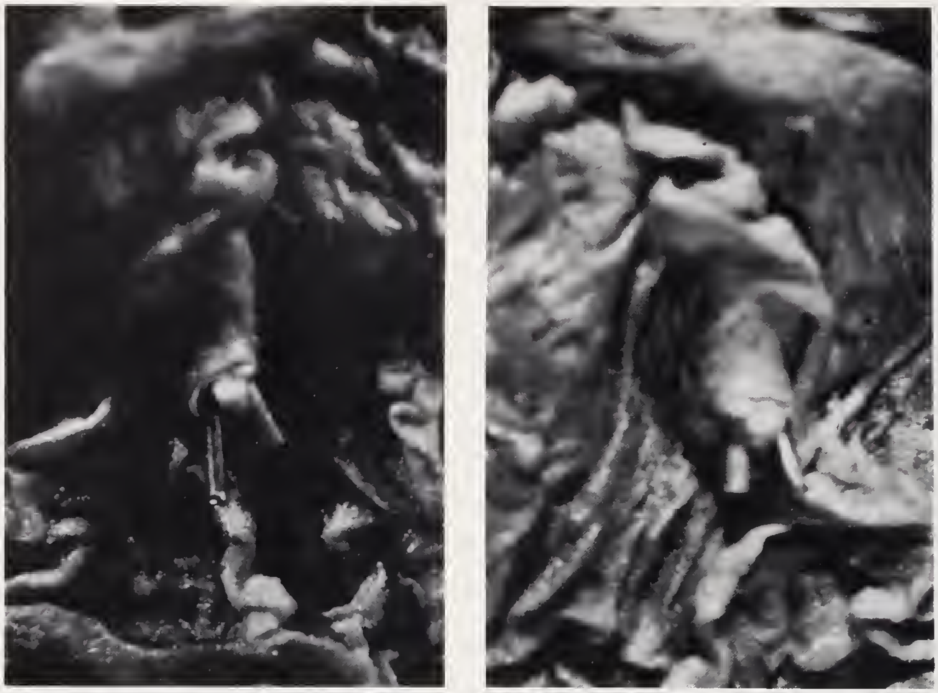

FIG. 4. "That two membranes hanging loosely." Andreas Vesalius, *De Humani Corporis Fabrica.* Personal observations 35 and 37.

(8), having examined exhaustively nearly 200 duodenopancreas sections (dissection with the aid of a magnifying glass, serial sections, Mallory staining technique, corrosion preparation, etc.). Concerning Santorini's valves, I have found them regularly in keeping with the descriptions given by their discoverer.

With respect to their functions, I consider them exactly in accordance with those assigned by Santorini, two centuries before Brown and Echen-

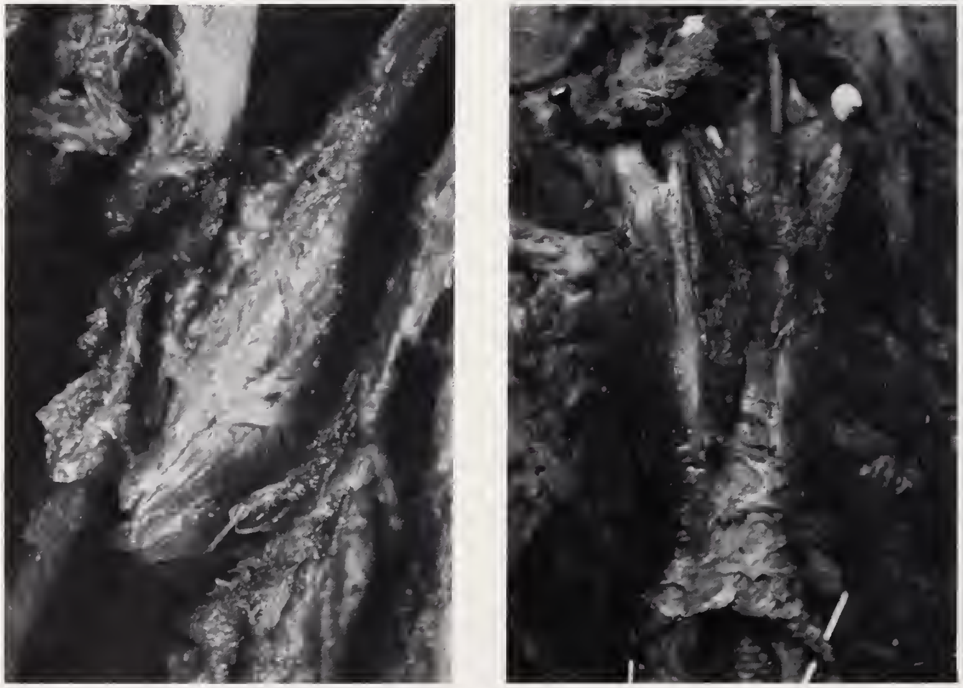

FIG. 5. Personal observations 35 and 37. The posterior side of the ampoule has been cut, allowing another view of the valves.

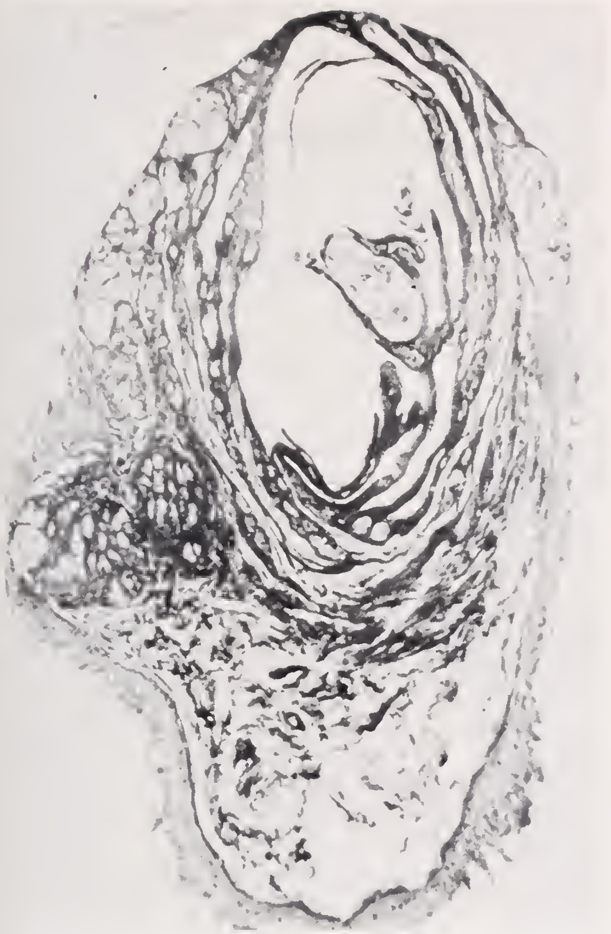

FIG. 6. The valves are seen after a transversal section of the duodenal end.

berg. According to our studies, the pancreatic duct is devoid of its own sphincter; neither do we recognize the existence of the so-called common sphincter of the ampulla or of the papilla. It is for this reason that I consider that Santorini's valves fulfil—as presumed by their discoverer—an important role in the physiology of the terminal portion of the choledochus and Wirsung's ducts (9–11).

Conclusions

1. The valves existing in the terminal ampulla of the choledochus and Wirsung's ducts are normal structures which, according to Schwegler and Boyden are detectable as early as the third month of fetal life.
2. Their functions are exactly in keeping with those assigned to them by their discoverer, Giovanni Domenico Santorini, in 1720.
3. It is for the foregoing reasons that they should be designated "Santorini's valves."

Acknowledgments

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Fatal Brain Abscess Following Periodontal Therapy: A Case Report

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Abstract

Brain abscesses occur by direct spread of an infection to the brain or secondary to hematologic spread as the result of bacteremia or septicemia. Mortality and morbidity remain high despite advances in neurosurgical care, diagnostic procedures, and antibiotic therapy. A case is presented of a healthy man who underwent drainage and currettage of a periodontal infection and developed a fatal brain abscess.

Introduction

Fatal complications from dental treatment are uncommon. Bacteremias occur after many dental procedures and may result in infectious sequelae, especially in patients having a history of rheumatic heart disease or previous episodes of endocarditis (1). Brain abscess formation from a bacteremia following dental manipulation is rare. This serious complication is most commonly described following recent tooth extraction (2) but has also been reported following restorative dentistry under local anesthesia (3), and has been associated with severe dental caries with multiple periapical pathosis (4). Presented is the case of a healthy man who was treated for a periodontal infection and developed a fatal brain abscess with a microbacterial content identical to that found in the oral cavity. A literature review revealed no other documented case of odontogenic brain abscess to have occurred secondary to periodontal therapy.

Case Report

On July 12, 1977 a healthy, 54-year-old male went to his dentist complaining of sensitivity around a left mandibular tooth. A periodontal abscess surrounding the mandibular left second premolar was deeply curetted and drained. The pulp chamber was not entered nor were any teeth extracted. Antibiotics were not administered or prescribed. That evening the man experienced shaking chills with an oral temperature of 39° C (102.2° F). Aspirin was self-administered and he was afebrile the next day. He remained well until 14 days after dental treatment when he developed headaches with involuntary twitching of the left facial and neck muscles.

He was brought to the emergency room at which time examination revealed a 96 kg (211 lb) alert and oriented 54-year-old male. The general physical exam was within normal limits. Neurologic examination revealed slow mental calculation and slight left-sided facial weakness. Previous medical history was unremarkable except for a documented penicillin sensivity. No other drug reactions or allergies were reported.

The patient was admitted to the hospital with a preliminary diagnosis of brain abscess. Dexamethasone, gentamycin, vancomycin, and phenytoin were begun parenterally. Laboratory tests including complete blood count, platelet count, prothrombin time, urinalysis, chest radiographs, 18-channel blood chemistry, and electrocardiogram were all within normal limits. Computerized tomography (CT scan) revealed a 3 cm intercerebral mass lesion in the right frontal lobe (Fig. 1). Transfemoral cerebral angiography showed an avascular mass with an attenuated irregular anterior lumen in the right posterior frontal lobe of the brain.

On July 28, 1977 the patient underwent a right frontal craniotomy for excision and drainage of the intercerebral abscess. Postoperatively he did relatively well, except for mild facial and extremity weakness. Organisms cultured from the

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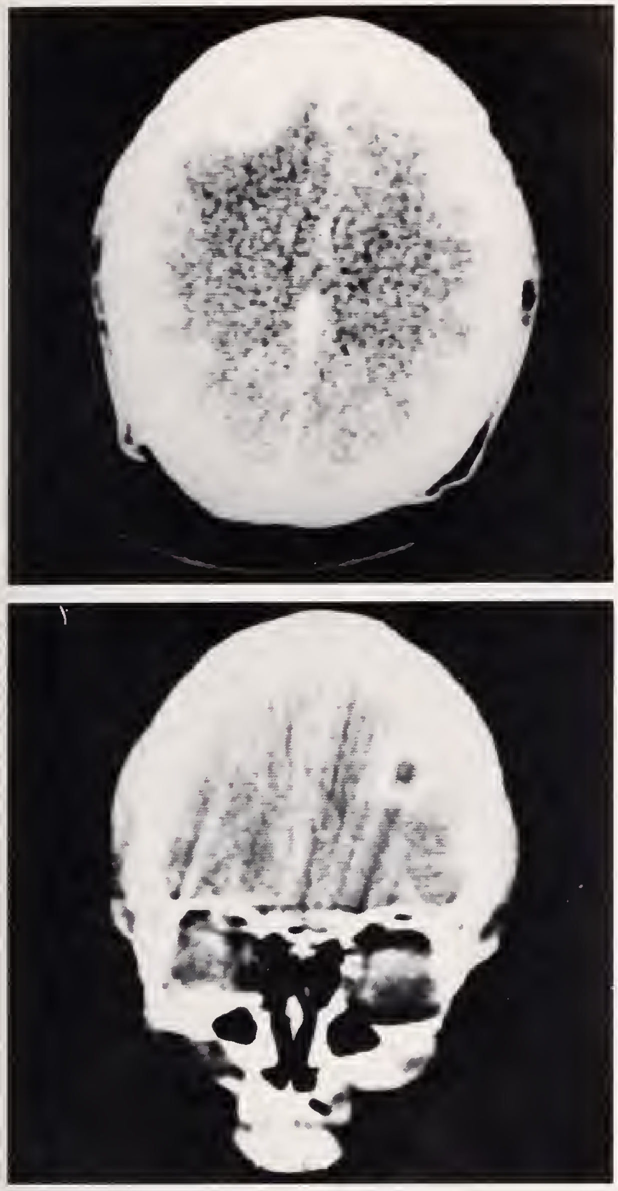

FIG. 1. Computerized tomography (CT scan) demonstrating an abscess in the right frontal lobe of the brain. A, coronal section. B, frontal section.

abscess were mixed anaerobes and aerobes that included *Staphylococcus epidermidis, Bacteroides melaninogenicus,* and *Streptococcus* species. Antibiotic therapy was changed to gentamycin and chloramphenicol.

On the sixth postoperative day, the patient's neurologic status markedly deteriorated. CT scan revealed marked cerebral shift from right to left due to cerebral edema. Dehydration therapy using mannitol resulted in temporary improvement of mental status and increased muscular strength on the left side.

Three days later the patient's neurologic condition again deteriorated. Repeat CT scan demonstrated an avascular mass lesion compatable with recurrence of brain abscess. He underwent a second craniotomy. There was a moderate subgaleal collection of foul smelling material. The abscess cavity was irrigated, debrided, and the necrotic bone flap was removed. Drains and catheters were left in place to permit postoperative irrigation and drainage. Direct cultures from debrided tissue grew *Staphylococcus epidermidis, Propionibacterium,* and *Bacterioides* species. Streptococci and gram negative bacilli were seen on Gram stain but failed to grow on solid media. Antimicrobial therapy was changed to tobramycin and chloramphenicol. Postoperatively, the patient was very alert, able to follow commands, was oriented to time and place, and moved his left upper and lower extremities better than during the preoperative period. Daily irrigation of the wound with bacitracin accompanied the parenteral medications. During the following days, there was marked improvement of the patient's mental status.

Several days later the area of cranial decompression was found to be bulging with purulent material draining through the penrose drain and a suture line.

On the fifteenth day following admission the patient became lethargic and markedly hemiparetic on the left. Streptococci were seen on Gram stain but failed to grow on media. He was again taken to the operating room for internal decompression of the right frontal lobe and evacuation of the subdural empyema. Tobramycin was discontinued and erythromycin infusions were begun because the infection did not appear to be subsiding.

Penicillin hypersensitivity tests were administered with negative results. Massive penicillin G infusions (2.5 million units per hour) were added to the chloramphenicol. There was no significant change in neurologic status. Hyperbaric oxygen therapy, which had continued since the second operation, was stopped.

Followup CT scan confirmed some improvement of cerebral edema and ventricular shift. Right-sided facial twitching was noted. Penicillin G infusion was reduced to 40 million units per day. Bloody serous drainage from around the urinary catheter was cultured and grew *Candida albicans.*

The following days again showed progressive deterioration of the patient's condition. On August 22, 1977 necrotic brain was found exuding from the craniotomy site. The patient's right pupil was dilated and would not respond to light but responded to mannitol therapy. His body temperature which had remained 37.5° C (99.5° F) until this time spiked to 39.5° C (103.1° F). Hemoglobin, hematocrit, and WBC were 10.7 g%, 31.2%, and 28,700/cumm respectively. After increased dosages of penicillin and chloramphenicol in addition to a blood transfusion the patient was afebrile the next day. However, liver enzyme titers became elevated and *Candida albicans* continued to be cultured from the urine. Neurologic status and vital signs remained unchanged.

CT scan on August 23, 1977 showed a right frontal mass. The patient became unresponsive to all stimuli, had a dilated right pupil, and was having periods of apnea. Cultures of wound irrigation fluids failed to grow any microorganisms, but *Candida albicans* remained in the urine. On August 25, 1977 the patient was taken to the operating room for the fourth time for removal of the right frontal lobe.

Postoperatively he was unresponsive to all stimuli. The pupils were asymmetric and sluggishly reactive to light. During the following days periods of apnea developed and the pupils became fixed and dilated. On August 31, 1977 the patient expired.

Discussion

Hematogenous spread of infection to the brain is well recognized especially when associated with congenital cyanotic heart disease and chronic pulmonary infections (5). Chronic otitic and paranasal sinus infections or trauma to the central nervous system may also predispose to a brain abscess. Headache and neurologic disorders, including seizures, are most frequently the initial signs of a brain abscess. Fever, increased leukocyte count, alteration of conciousness, and hemiparesis may not be present during the early stages of the infection. Symptoms appear within several weeks to months after the primary infectious process, but years may pass before a neurologic deficit is noted (6).

Facial infections spread to the brain by direct invasion or dissemination through small blood vessels, that is, cavernous sinus thrombosis. The importance of hematogenous metastasis even from apparently contiguous foci is emphasized by the occurrance of otogenic brain abscesses without meningitis and multiple discrete brain abscesses originating from the frontal sinus (7). It is believed that curetting the septic gingivae surrounding the left mandibular premolars caused a bacteremia that localized in the right frontal lobe of the brain. Direct intracranial invasion of bacteria from the left mandible crossing the midline is unlikely if the local vascular and lymphatic drainage is considered.

Microorganisms most frequently cultured from brain abscesses when an oral infection is the suspected etiological factor are *Streptococcus viridans,* Streptococcus group F (anaerobic), *Hemophilus parainfluenzae, Corynebacterium* species, *Propionibacterium acnes,* and *Bacterioides* species (8). Anaerobic growth is favored in infarcted brain because of low oxygen tensions. Anaerobic streptococci may be particularly destructive to brain tissue which accounts for the higher mortality and morbidity in patients from whom these organisms have been isolated compared with patients having brain abscesses not containing streptococci. One report found that anaerobic bacteremia occurred after 12% of cases following tooth extraction (7).

Prophylactic antibiotics used during periods of bacteremia may prevent focal colonization within the brain and are indicated in patients having cyanotic heart disease, a history of rheumatic heart disease, pulmonary infections, and altered host resistant states. Antibiotics used to treat dental infections may be sufficient to cure the peripheral infection but not the brain abscess, necessitating careful followup in patients treated for an infectious process (9).

Treatment of brain abscesses is complicated and involves antimicrobial therapy and surgical excision or drainage. The mortality rate remains high despite specific antibiotic therapy. Likewise, patients who recover may suffer permanent neurologic deficits including motor and sensory dysfunctions, aphasia, and seizure disorders. Early clinical recognition of the disease and immediate therapeutic intervention provide the patient with the most favorable prognosis.

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The Effect of Raw Soybean on Exocrine Pancreatic Secretion in the Dog

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DAVID A. DREILING, M.D.

The effect of long-term soybean feeding on pancreatic growth and function in animals has been controversial. The purpose of our study was to monitor the exocrine pancreatic secretion and histology of the pancreas in dogs fed a diet containing 15% by weight raw soybean.

Materials and Methods

A group of adult dogs, weighing 15–25 Kg were used. Each dog had a Thomas Cannula inserted into the duodenum opposite the main pancreatic duct opening. The accessory pancreatic duct was ligated and transected, and a gastric cannula was inserted in the most dependent part of the stomach to drain gastric secretion externally. At this operation, a pancreatic biopsy was taken as well.

Two weeks following surgery, the resting pancreatic secretion as well as the secretin-stimulated (1U/Kg) secretion of the conscious animals, were collected and examined for volume, (HCO_3^-), Cl^-), and protein (enzyme), concentration and output.

The secretin used was secretin (BOOTS) given as a single I.V. bolus. Pancreatic secretions were collected from each dog by placing glass cannulas (2 mm diameter) into the main pancreatic duct through the Thomas Cannula after the stomach contents were drained out. The resting pancreatic secretion was collected for a period of ten minutes. After the injection of secretin, three 15 minutes samples were analyzed.

To calculate the bicarbonate and chloride, a Beckman-CO^2, Chloride-Analyzer was used. The Roche Amylochrome Method was utilized to determine the total proteins (amylase).

The secretin tests were repeated. Reproducible and constant results were achieved. Then the dogs were fed a diet containing 15% by weight raw soybean mixed with Canine Maintenance Science Diet T.M. (100 gr of soybean contains about 1200 mg of trypsin inhibitors) (4, 5), for 16 weeks and a repeated examination was made of the resting as well as the secretin-stimulated pancreatic secretion at 2, 4, 6, 8, 10, 12, 14, and 16 week intervals.

The raw soybean used was the "natural" and not the "special," that has to be kept at 4°C in 70% humidity and periodically checked for oxides in order to avoid contamination with Salmonella free-macrotoxin and antitoxin, which could lead to the formation of nitrosamines which are potential carcinogens.

Each dog served as its own control and after 16 weeks, another pancreatic biopsy was taken.

Results

Figure 1 summarizes the results of volume and bicarbonate secretions in the resting as well as under secretin stimulation before and during soybean feeding.

Figure 2 shows the resting as well as the secretin stimulated pancreatic enzymes concentration before and after soybean feeding.

Figures 3 and 4 compare the results for volume, bicarbonate concentration and bicarbonate secretion, at the resting as well as the secretin stimulated state, before and during feeding.

The data indicate no alteration in unstimulated as well as stimulated pancreatic flow, bicarbonate concentration enzyme production, or bicarbonate output. Autopsy and histologic sections obtained from the pancreas of the experimental animals disclosed no structural changes.

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This work was supported by the Alfred and Florence Gross Research Fund.

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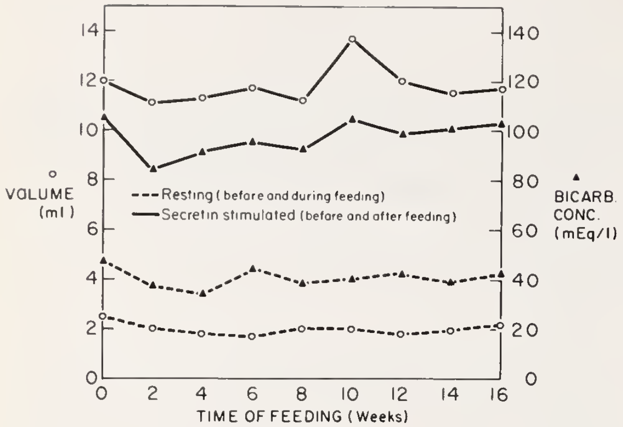


FIG. 1

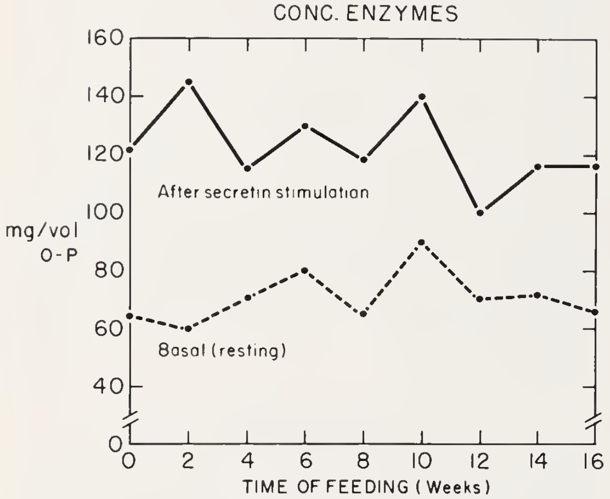


FIG. 2

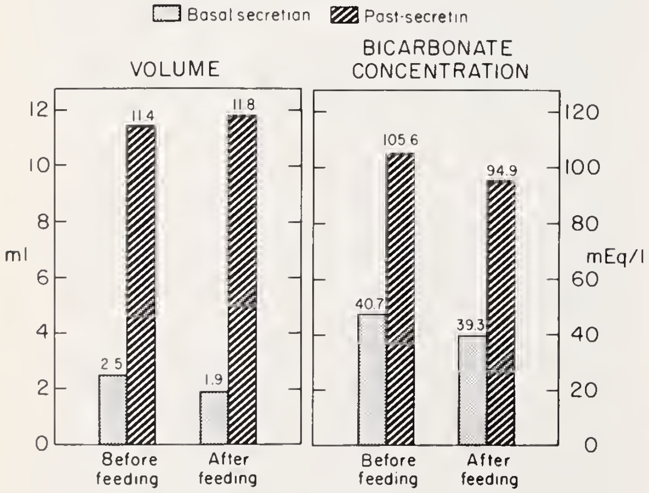
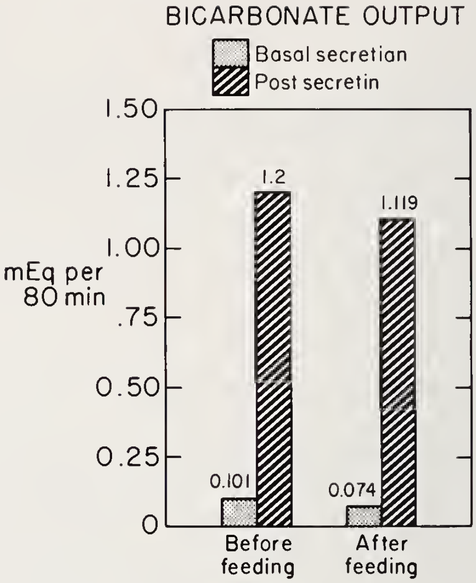


FIG. 3



Discussion

The present studies were undertaken to furnish support that soybean ingestion may serve as a cocarcinogen in the development of pancreatic cancer: the thesis being induced hyperplasia, hypertrophy, and hypersecretion furnishing a favorable milieu for ingested carcinogens in the diet.

The effect of long-term soybean feeding on pancreatic growth and function in animals has been controversial. Rackis and McGee (4), found that the pancreatic hypertrophy that occurs in rats fed raw soybean, was reversed by switching the rats to control diets or to diets containing 30% toasted defatted soy flour. Patten et al (1), working with adult male and female mongrel dogs, concluded that 15% to 30% dietary raw soybean did not significantly alter the cellular structure or weight of the pancreas. The synthesis of trypsinogen, chymotrypsinogen and lipase was temporarily impaired; but these syntheses returned to normal. Different results were obtained by Haines (6), working with rats and Alumot (7), working with chicks. They found that young rats and chicks fed raw soybean develop pancreatic hypertrophy, hypersecretion of pancreatic enzymes, as well as suppression of growth. However, adult rats and chickens are less affected by the diet. Gorril and Thomas (2) and Hooks et al (3) reported that calves and growing pigs fed raw soybean did not develop pancreatic hypertrophy or hypersecretion of pancreatic enzymes.

The discrepancy in reported results may reflect the existence of one or more of the following mechanisms or factors:

1. The effects of raw soybean might be dependent on the age and species of animal used.
2. The presence of a pancreaticothrophic

substance in the soybean given to the animals.

3. The release of endogenous pancreozymin, due to the same factor.
4. The existence of negative feed-back inhibitor mechanism in certain species of animals.

We were not able to produce either pancreatic structural changes or modifications in the exocrine pancreatic function in our group of dogs after a long-term (16 weeks) raw soybean feeding, the same result that Patten (1) obtained in his studies. In comparing our results with the results of the other authors (2–4, 6, 7), we think that several factors might be involved:

1. The existence of an unknown pancreatic endogenous mechanism that protects the pancreas against the effect of raw soybean, which has been demonstrated in other species of animals.
2. The raw soybean used (Natural), may not have either a trophic or carcinogenetic effect.
3. 16 weeks of feeding time may not be long enough to incite structural or secretory pancreatic alterations.

Conclusion

These studies indicate that long-term raw soybean feeding does not alter the exocrine pancreatic function of the unchallenged canine pancreas. The dogs did not develop gross, structural alterations or microscopic changes in the pancreas.

In the procotol and experimental animal use, there is no evidence to link soybean ingestion to pancreatic cancer.

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Neurologic-Neurosurgical Notes

Allan E. Rubenstein, M.D. and Martin H. Savitz, M.D., Coeditors

Recovery without Surgery from Uncal Herniation and a Decerebrate State with Fixed, Dilated Pupils

JOHN PETER LIU, M.D.

Abstract

A 62-year-old female, with a right temporal mass lesion angiographically characteristic of a glioblastoma, recovered from uncal herniation without surgical decompression. Acutely, she developed fixed dilated pupils, absent oculocephalic reflexes, and decerebrate posturing. Following the use of mannitol and dexamethasone, she recovered with modest neurologic deficit. Computerized axial tomographic (CAT) scan revealed extensive right to left midline shift and right ventricular compression. To our knowledge, this is the first documented case of such recovery without surgical intervention.

In adults, uncal herniation from supratentorial mass lesions progressing to decerebration with fixed, dilated pupils and absent oculocephalic refluxes typically leads to death or a vegetative state. We report an adult with a cerebral mass lesion, presumed glioblastoma, who suffered uncal herniation. Despite progression to severe midbrain dysfunction, she recovered after mannitol and dexamethasone therapy with modest neurologic deficit. No surgery was performed.

Case Report

A 62-year-old female was admitted April, 1980 with the complaint of bifrontal headaches for two weeks. An outpatient computerized axial tomographic (CAT) scan had revealed a right temporal lobe mass lesion. On the day of admission, she was completely alert and had a normal neurologic exam. Carotid angiography revealed vascularity of the lesion characteristic of a glioblastoma of the right temporal lobe. The next day, she was somnolent, vomited and became unresponsive. Her right pupil was fixed to light and dilated and she had a pulse of 48. Despite immediate administration of 20 mg% mannitol and 20 mg dexamethasone intravenously, she became apneic and was intubated. She deteriorated to a state of bilaterally fixed and dilated pupils, absent oculocephalics reflexes, shallow respirations of 16 per minute and decerebrate posturing to sternal pressure. An electrocardiogram revealed normal sinus rhythm with ST depressions of the lateral precordial leads and an arterial blood gas on room air during the acute decompensation was pH 7.46, pCO_2 30.7 mm Hg and pO_2 65.9 mm Hg.

One and a half hours later, she was noted to have spontaneous movements of all extremities with appropriate response to noxious stimuli. Her left pupil had constricted to 2 mm though her right pupil remained fixed at 5 mm and oculocephalic reflexes were still bilaterally absent. Seven hours after the acute event, she was able to speak and could reverse serial order such as spelling C-A-T backwards. She was oriented to person and time. The next day she followed two step commands. Bilateral ptosis, right greater than left, was noted. The right pupil was 5 mm and still fixed to light, the left was 2 mm and reactive. The right eye was laterally deviated with minimal movement in all other directions indicating a right oculomotor nerve paresis. The left eye was midline and paretic in all directions of gaze. A CAT scan that day revealed a right sided tumor with extensive edema, midline shift, and ipsilateral ventricular compression (Fig. 1).

She continued to improve. Ultimately, she be-

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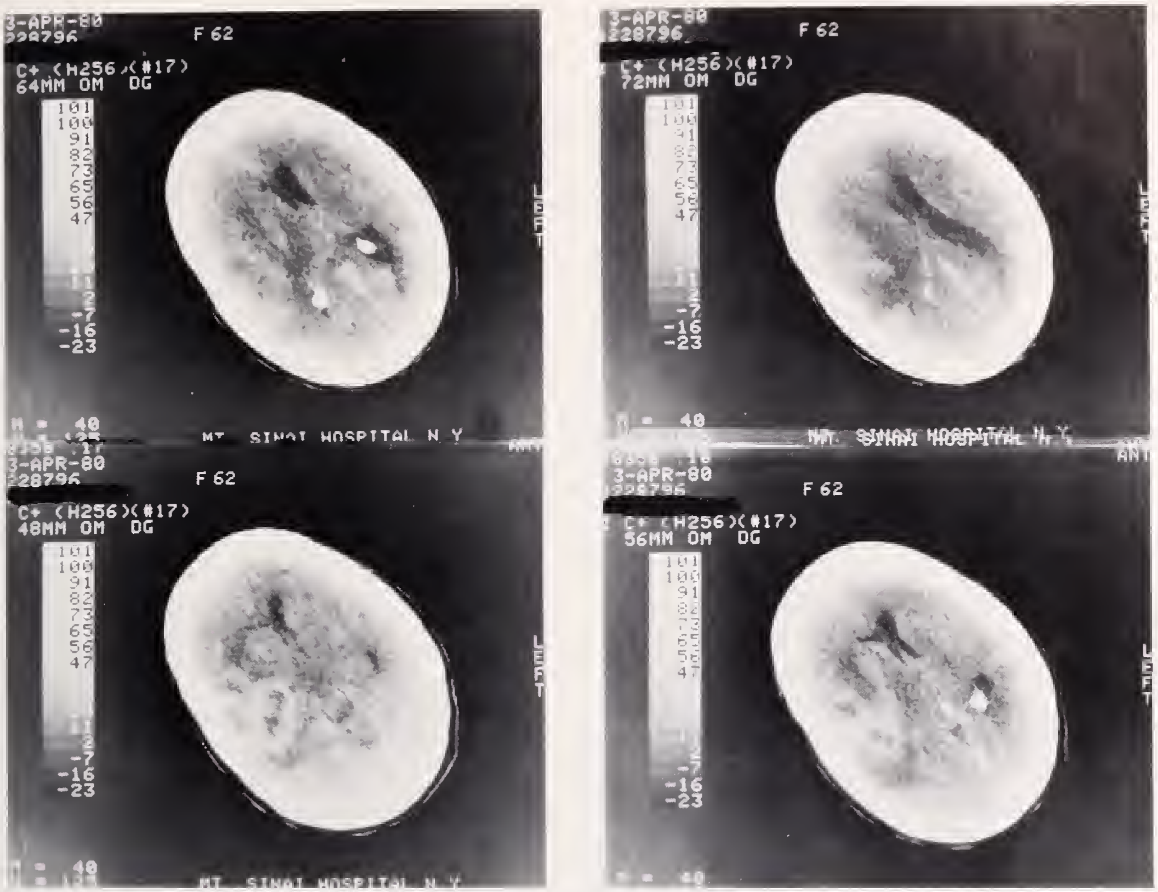

FIG. 1. Postcontrast CAT scans demonstrating a right temporal mass lesion with prominent midline shift and compression of ipsilateral ventricles.

came oriented and alert but was still unable to reverse the spelling of the word H-A-N-D. Speech was animated and appropriate. Paresis persisted in the right third nerve. Right ptosis was much improved and that of the left eye had completely resolved. The right pupil was 4 mm, the left 2 mm and both were reactive to light. The left eye had only mild limitation of gaze in all directions. Fundi were normal. There was a left homonymous field deficit and a mild left facial paresis. She had a slight left hemiparesis and a left greater than right sided dystaxia. Sensory exam was normal. She could walk with personal assistance and a walker. She was discharged on dexamethasone seventeen days after the acute herniation episode. She refused radiation therapy. Three months later she was still alive and living at home.

Discussion

Transtentorial herniation leading to fixed, dilated pupils, absent oculocephalic reflexes and decerebrate posturing carries a grim prognosis in adults (1–4). Those few cases of survival reported in the literature uniformly followed surgical decompressive procedures (5–8). To our knowledge, this is the first described case of survival without surgery in an adult who manifested severe midbrain dysfunction subsequent to uncal herniation.

Plum and Posner (1) report that in their adult patients in whom "midbrain signs were fully developed, most have either died or remained in coma for months until transferred for custodial care." Bricolo et al (2) in a study of 149 head trauma victims who exhibited deep coma with decerebrate posturing and fixed gaze related that 144 died. All patients, including the five survivors, were treated surgically if angiographically indicated. Overgaard et al (3) and Vapalahti et al (4) report that decerebration in adult head trauma patients is an "overwhelmingly bad prognostic sign" without hope of recovery.

All described cases of recovery in adults over thirty-years old from uncal herniation with midbrain dysfunction in association with supratentorial compressive lesions have followed surgical therapy. In 1952, Freedman (5) reported nineteen patients, two with temporal lobe tumors, who recovered after surgery from coma with decerebration. Similarly in 1970, Brendler and Selverstone (6) reported nine patients with supratentorial mass lesions who recovered after surgery from coma with decerebration and fixed, dilated pupils. Recently, two additional cases of surgical decompression and recovery from uncal herniation complicating acute subdural hematomas have been reported (7, 8).

Our patient received a total of 500 cc of 20 mg% mannitol intravenously and was subsequently maintained without surgical intervention on dexamethasone 4 mg every six hours. Only a single bolus of mannitol was given and no rebound deterioration occurred. One and a half hours after initiation of therapy, clinical improvement was evident. This response is consistent with the findings of Shenkin et al (9) of a maximal cerebrospinal fluid pressure reduction at one to two hours after mannitol bolus. Burton et al (10) noted a maximal reduction of cerebrospinal fluid pressure with mannitol at three to four hours with a duration of effect for six to eight and a half hours without a rebound effect. Since clinical improvement of cerebral edema with dexamethasone becomes evident at twelve to forty-eight hours (11), it is unlikely that dexamethasone was responsible for the initial improvement of our patient. Maximal steroid improvement of cerebral edema may be delayed up to two weeks (11).

Summary

In summary, we present a rare case of nonsurgical reversal of uncal herniation with fixed dilated pupils, absent oculocephalic reflexes, and decerebrate posturing in an adult with presumed glioblastoma multiforme. Mannitol and dexamethasone should be administered at the first signs of transtentorial herniation from supratentorial mass lesions. Improvement with stabilization may be witnessed within hours without subsequent rebound deterioration and surgical intervention in cases of underlying neoplasms may not necessarily be indicated.

Acknowledgments

The author thanks Morris B. Bender, M.D. and Melvin D. Yahr, M.D. for reviewing the manuscript.

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Presumptive Myelopathy Following Varicella

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Abstract

One week following the onset of varicella, a 20-year-old man was admitted with the chief complaint of urinary retention. He subsequently developed bilateral extensor plantar responses without demonstrable motor or sensory dysfunction. The urinary retention resolved over a two-day period. The nature of this case of presumptive varicella myelopathy is contrasted with previously reported cases. The features of this case help to demonstrate a clinical spectrum of myelopathy following varicella.

Varicella is a common childhood disease which is rarely associated with neurologic complications, the incidence ranges from 3% to 5%. (1–8) The conditions have been categorized by Johnson and Milbourn (7) into four major clinical types: 1) cerebral encephalitis, 2) cerebellar, 3) aseptic meningitis, and 4) myelopathy. Of these four types, the latter two are very uncommon; the myelitic form was represented by only a single case in their series. The clinical presentation and course of the prior reported cases of varicella myelopathy have been remarkably similar.

Case Report

A 20-year-old right-handed Cuban male went to the emergency ward of the City Hospital at Elmhurst because he had not been able to void for sixteen hours. One week prior, he had vesicular lesions on his chest accompanied by fever. Over the following days the lesions spread and his temperature was as high as 40 degrees C (oral). There was no prior history of varicella.

On admission, the patient had a temperature of 38.5 degrees C (oral). The physical examination revealed generalized vesicular lesions, typical of varicella, in varying stages of crusting. The remainder of the examination was unremarkable. Neurologic examination demonstrated an alert and oriented male. Cranial nerve testing was normal and there was no papilledema. Muscle power was strong and equal, tone was normal. Sensory examination showed intact sensation to all modalities over the entire body, including the perianal area. Reflexes were present and symmetrical; responses to plantar stimulation were flexor bilaterally. Cremasteric abdominal and bulbocavernosus reflexes were all present. There was no demonstrable ataxia. A foley catheter was inserted and 600 cc of urine was drained before the catheter was clamped.

Admitting laboratory examination was as follows: hemoglobin 14.8%, hematocrit 45%, white blood cell count 9500 (differential: polys-63, bands-2, lymphs-27, monos-6, eosins-2). The sedimentation rate was 42 mm/hr, six and twelve channel chemistries were normal, and urinalysis was unremarkable. Radiographs of the chest and entire spine were within normal limits.

Hospital Course

Approximately eight hours after admission, the patient was noted to demonstrate a right extensor plantar response; the remainder of the examination was unchanged. The following morning, in addition to the right extensor plantar response a left extensor plantar response was present. Testing of muscle strength and sensation was still normal. The patient continued to need catheterization for urinary drainage. On the second day

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the patient was able to void voluntarily; subsequently, bladder function remained normal.

Later in the day a lumbar puncture was performed which showed an opening pressure of 100mm H_2O, normal manometrics, and clear fluid. Cerebrospinal fluid studies: cell count 9 WBCs (100% lymphs) and 5 RBCs; protein 27 mg/dl and glucose 61 mg/dl. Cultures of fluid for bacteria, AFB, fungus, and virus were negative.

On the third hospital day extensor plantar responses were still present; the patient was discharged. Follow-up examination ten days after discharge was normal and no extensor plantar responses were elicited. An additional examination one month later was again normal.

Discussion

The occurrence of myelopathy following varicella constitutes a rare phenomenon. The seventeen cases summarized in Tables I and II (based on but modified from that of White (3) and Sinniah (6)) including our own case, represent all reported cases from the year 1915 to the present. Ten of these cases may be considered purely myelitic (Table I); seven cases which are predominately myelitic (Table II) but with an encephalitic component (three cases) (7, 16, 19), meningeal features (two cases) (4, 15), or optic nerve involvement (two cases) (17, 18). We consider these two groups (the purely myelitic and the predominately myelitic) to be similar in nature and therefore will discuss them together.

In most cases, the affected individual is a young person, usually male, age range from three to 20 years with the exception of one patient who was 34 years. (17) Symptoms of myelopathy developed from four to 15 days after the onset of the rash. The neurologic symptoms never evolved before or coincident with the appearance of the eruptions. Out of the group of 16 patients reported before ours, there was a paraparesis evident on examination in 11, a triparesis in three, and quadriparesis in two. The character of the paresis was spastic in six instances, flaccid in five, and not mentioned in five. Five of the patients with the purely myelitic form demonstrated sensory impairment manifest as a sensory level, most com-

TABLE I

Summary of Purely Myelitic Cases

Author	Age	Sex	Latency Period	Signs & Symptoms of Spinal-Cord Involvement	Sphincter Involvement	Cerebrospinal Fluid Findings	Course & Follow-up Result
Smith[9]	7	M	13	Spastic paraplegia; paresis of left arm; bilateral Babinski signs; loss of sensation both legs.	Urinary retention	"Normal"	In 1 yr. able to "play freely" res dual spasticity and bilateral Babin ski signs; sensation normal.
Giraud et al[10]	3	M	9	Flaccid paraplegia with active reflexes and bilateral Babinski signs; paralysis of right arm; thoracic breathing.	Urinary retention	50 wbc/cu mm Protein positive	Examination normal in 20 days.
Paine & Byers[11]	8	M	16	Spastic paraparesis with bilateral Babinski signs.	(yes)	Approx 16 wbc/cu mm Protein 40 mg/dl	Completely normal within 10 days
White[3]	12	F	5 (14)	Spastic paraparesis with bilateral Babinski signs. T4 sensory level, incomplete.	Urinary retention	129 wbc/cu mm 83 lymphocytes Protein 40 mg/dl	Regained sphincter control and abl to walk with slight spastic gait i 20 days. Examination normal i one month except for hyperactiv knee and ankle reflexes.
Pitner[12]	30	F	9	Spastic paraparesis with bilateral Babinski signs.	No	2 wbc/cu mm Protein 46 mg/dl	Ambulatory, without aid in 4 days Examination normal in 10 days, ex cept for bilateral Babinski signs Complete recovery at 1 year.
Sinniah[6]	9	M	4	Flaccid paraplegia with areflexia. Bilateral Babinski signs at 1 month. T8 sensory level.	Urinary retention with overflow incontinence	4 wbc/cu mm Protein 90 mg/dl	Ambulatory with crutches after months. Residual spasticity an weakness in both legs with bilater al Babinski signs at end of one year
Shah[8]	14	M	10	Flaccid paraplegia; with areflexia; bilateral Babinski signs; T8 sensory level.	Urinary retention then incontinence	3 wbc/cu mm (100% lymphocytes) Protein 30 mg/dl	No improvement at 2 weeks. N further follow-up.
Nigam[13]	9	M	8	Paraplegia with areflexia; bilateral Babinski signs; T10 sensory level (complete).	Urinary retention then overflow incontinence	4 wbc/cu mm (100% lymphocytes)	Complete recovery in 14 months.
Warrier[14]	17	M	9	Paraplegic plus one arm; brisk reflexes; bilateral Babinski signs; T10 sensory level.	Urinary retention	26 wbc/cu mm 100% lymphocytes Protein 96 mg/dl	No follow-up.
Current Case	20	M	7	Right then left Babinski sign.	Urinary retention	9 wbc/cu mm 100% lymphocytes	Normal examination at 10 days.

TABLE II
Summary of Predominately Myelitic Cases

Author	Age	Sex	Latency Period	Signs & Symptoms of Spinal-cord Involvement	Sphincter Involvement	Cerebrospinal Fluid Findings	Course & Follow-up Result
Krabbe[15]	8	M	10	Flaccid paraplegia with areflexia in legs; bilateral Babinski signs; T4 sensory level; vomiting, restlessness, neck stiffness.	Urinary retention	37 wbc/cu mm Protein 40 mg/dl	Bladder function returned in 10 days; spasticity with increased reflexes appeared; normal examination at 52 days.
Wilson & Ford[16]	3	M	7	Spastic paraplegia with increased reflexes in legs; no Babinski signs; sensation normal; "drowsy."	Sphincter control diminished	Not reported	Movement of legs returned in 4 days; slight stiffness of both legs and active reflexes in six weeks.
Heller[17]	34	M	9	"Some paresis of both legs;" increased reflexes; bilateral ankle clonus and Babinski signs; hypothesia below L2; hyperesthesia of chest and back between clavicle and lower rib border; neck stiffness and optic neuritis.	Urinary retention	Not reported	Ankle clonus and Babinski sign on left, with slight weakness of left leg at 19 days.
MacIntyre & Beach[18]	7	F	7	Paraplegia with hyperreflexia in legs; T11 level; 8 days after onset unable to move arms, with blunting of sensation in arms; left optic neuritis.	Not reported	Not reported	Vision returned in 6 days; arms normal in 15 days; normal examination in 8 months.
Beer[19]	7	M	12	Paralysis of arms and legs with spasticity and bilateral Babinski signs; 1 focal convulsion.	Loss of sphincter control	Not reported	Complete recovery except for slight limp in 1 month.
Johnson & Milbourn[7]	9	M		Paraparesis with bilateral ankle clonus; normal reflexes; absent Babinski signs; no sensory findings reported; headache and vomiting.		31 wbc/cu mm (100% lymphocytes) Protein 40 mg/dl	Improved at 11 days; normal examination at 3 weeks but complained of limp; perfectly well at 6 months.
McCarthy & Amer[4]	9	F	15	Ascending flaccid paralysis; T4 sensory loss with hyperesthisia involving chest, neck, arms. Vomiting, stiff neck, headache.	Urinary and fecal incontinence	1st LP normal 2nd LP 24 hrs. after admission 40 wbc/cu mm (40% monorytes) Protein 72 mg/dl	Urinary bladder dysfunction and bilateral lower extremity paresis at 47th day; 2 years later, mild bilateral foot drop and occasional urinary bladder dysfunction. Treated with cortiosteroids.

monly in the thoracic region. In the predominantly myelitic form, four patients had sensory levels (thoracic in three), two had no abnormalities of sensation and in one patient there was no mention of a sensory examination. The two patients with optic neuritis and the patient with an ascending flaccid paralysis had, in addition to a sensory level, other abnormalities of sensation suggesting a radiculitis or a peripheral neuritis as well. Micturition disturbances were an almost constant finding, and were present in all but three patients.

The outcome of post-varicella myelopathy seems generally favorable for either group. Complete or near complete resolution of symptoms within 14 months was the course in six of the ten cases with the pure myelitic form and in five of seven cases which were predominantly myelitic. The severity of the neurologic impairment had no predictive value with regard to outcome; of these 11 cases with good recovery, five had been paraplegic and complete recovery was seen as early as 20 days. Two of the prior case reports (4, 6) have questioned the effectiveness of steroid therapy in post-varicella myelopathy. The two cases which were steroid treated showed little improvement (4, 6). In view of the spontaneous improvement seen in most of the reported cases, steroid therapy does not appear to offer any advantage.

The clinical picture of our patient is unlike other reported cases of varicella myelopathy. The initial symptom was urinary retention. Subsequently, bilateral extensor plantar responses were noted without change in muscle strength, tone or sensation. The urinary retention resolved over a two-day period; the patient was virtually asymptomatic thereafter and the extensor plantar responses disappeared at ten days. Thus, a benign and transient course as represented by our patient appears to represent one end of the spectrum of varicella myelopathy.

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Erratum

In the January/February 1981 issue, "Theodor Billroth: The Life of a Surgeon in the Spirit of Music" by Christian Holinka, Ph.D. The first seven lines of the second column on page 31 were incorrect. That section should read:

> "Enlightenment, was not directed at their metaphysical system, but at their attempt of analyzing such a system by pure reason, when in reality man lacked the faculties for analysis of the mechanisms behind his reasoning. Thus, according to Kant, a philosophy of metaphysics inevitably becomes speculative."

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BERNARD S. WOLF, M.D.
1912–1977

By
Harold G. Jacobson, M.D.

It is fitting that Mount Sinai Medical School of The City University of New York should be honoring Bernie Wolf, since this school and this hospital were enormously meaningful and important to him. Bernie possessed an incredibly probing and facile mind. He was not content to be a scientific spectator. His talents and contributions as a superb physician, a dedicated teacher, a prodigious investigator and gifted and prolific writer, have well established him in the front ranks of the great leaders of the radiologic world.

Dr. Wolf was born in 1912 in New York City and was educated in the New York City public schools. He matriculated at New York University, with a degree in physics and major credits in mathematics and chemistry. All this provided the background for his later work. He earned an M.D. degree from the same University in 1936. That he was truly brilliant was obvious. He was elected to Alpha Omega Alpha and was awarded the Luigi Salerno medal in Pathology in medical school.

He came to The Mount Sinai Hospital in 1936 and was a house officer through 1940. He began as an intern in pathology and bacteriology for one year and then served for three years as a rotating house officer. He pursued his residency program in radiology from 1940 through 1942 at Mount Sinai and was certified by the American Board of Radiology in 1942. He then assumed the position as assistant radiotherapist from 1942 through 1944 in The Mount Sinai Hospital. Bernie married Isabel, May 4, 1939. Two wonderful children were born of this couple—Ellen who is also a radiologist and Susan who is living in California.

Dr. Wolf entered the U.S. Army with the rank of Captain in 1944 and was assigned as a health physicist in the Manhattan district. He worked on the development of the original atomic bomb and was one of the first physicians to enter Hiroshima at the end of the war to determine residual radioactivity.

After the war, he returned to the Mount Sinai Hospital in the capacity of associate radiotherapist for two years and simultaneously served as the Director of the Atomic Energy Commission in the New York City office. In 1949, he was appointed Director of the Department of Diagnostic Radiology at this hospital to replace Dr. Marcy L. Sussman. When the medical school was started at this great institution, he became Professor and Chairman of the Department of Radiology in 1966. He retired from the chairmanship while continuing as Professor of Radiology shortly before his death on the 16th of September, 1977.

Bernie Wolf was a member of the usual radiologic and other medical scientific organizations. He was past president of the New York Roentgen Society, a member of the Mayor's Advisory Committee on Radiation for the City of New York, subcommittee on human applications of radioactive materials, special committee on radiologic aspects of Civil Defense for New York City and a consultant to the Atomic Energy Commission for a decade, from 1949–1959. He was assistant editor of Gastroenterology from 1960 to 1965 and served on the editorial staff of Journal of The Mount Sinai Hospital (now called The Mount Sinai Journal of Medicine), being the founder of the Radiology Notes.

Bernie Wolf made many significant contributions to radiologic literature, covering almost every area in this discipline. These included radiologic physics, obstetric and gynecologic radiology, plain film diagnosis of the abdomen, cardiovascular radiology, and neuroradiology. Two hundred articles and one textbook were the result of the prodigious efforts of this unique man. Noteworthy among his more important contributions was his description of the importance of the vasculature of the posterior fossa in its applications to the diagnosis of even very small lesions in this area. Of similar importance was his work in the gastrointestinal tract, particularly related to the physiologic and anatomic details of the esophagus and the various aspects of inflammatory diseases of the colon.

Dr. Wolf held many prestigious offices and won many honors—too numerous to list. Among these was the Jacoby Medal awarded by The Mount Sinai Hospital – shortly before his death – a hospital in which he worked virtually his entire professional life. He was constantly in demand as a gifted teacher and was a highly popular visiting professor and a frequent participant in postgraduate courses. He was asked to give a large number of important named lectures as a reflection of his unusual teaching talents.

His sharply-honed analytical mind continually challenged him toward the new and the exciting. He simply had to know what it was all about. How did it work? Was it helpful? Thus it was no surprise that computerized tomography and ultrasonography should have intrigued him in the final years of his life. As in everything else that he undertook, he trained himself to become so adept in these two new revolutionary modalities, that before long his expertise in these fields was recognized on the level that matched his extraordinary abilities in neuroradiology and in the radiology of the gastrointestinal tract.

In all, Bernie possessed a true passion for full living. He enjoyed everything with a rarely encountered zest to spend time meaningfully. This prodigious worker somehow found the time to enjoy a host of nonmedical activities. He read voraciously, both in and outside of medicine. He loved and knew opera well and the theatre enthralled him. He was a gifted photographer, even with the simplest of equipment. He had a love for many sports, for example baseball, football, and hockey. Those who knew Bernie intimately were indeed blessed. Beneath his facade of dignified reserve, he was a warm, sympathetic and an empathetic individual with an innate decency, compassion and a genuine concern for all less fortunate than he. You could talk with him and to him and you knew that he was listening. He was a valued confidant whose wise counsel was always appropriate and rational. He possessed a sense of propriety and tolerant forebearance for the foibles and frailties of others. For being human and humane he knew that perfection was desirable, but did not exist. A friend and colleague recently wrote to this author about another giant in radiology who had recently died and the words are appropriate for Bernie. "He was the standard for the rest of us—the kind of human being we try to emulate, knowing full well that we cannot succeed, but being ashamed at not trying. Many times when puzzling over a case or seeing a beautiful sight or thinking about some political question I have wondered what would he say about this? No more the question and we are so much the poorer. We had the good fortune at least to walk for awhile in the same direction. He was the best I have ever known."

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The Role of Cardiac Catheterization and Angiography

Richard Gorlin, M.D.

Despite the significant advances in noninvasive testing in the diagnosis of coronary artery disease, there is still a role to be played using cardiac catheterization and coronary angiography. Despite the enthusiasm for ways to avoid cardiac catheterization, there are, nonetheless, over 50,000 catheterizations performed each year. Translating this into health care economics one can quickly figure out how many millions of dollars are spent on cardiac catheterization annually. The question that must be answered is how much of this is really worthwhile for the patient.

The first question to be addressed concerning coronary arteriography is the quality of the information that will be obtained. The development of the Cesium iodide x-ray tube has permitted a level of image resolution that simply did not exist before. This technologic advance enables one clearly to visualize the very fine ramifications of the coronary arterial tree down to 100μ in size. The degree of resolution and the type of information it provides permit quantification heretofore not possible.

Should the indications for catheterization and angiography be changed? Aside from the improvements just mentioned and the improvements in the safety of the procedure, the limited potential of noninvasive testing must be considered. Although there are many positive aspects of noninvasive testing, there are questions that still cannot be answered by this approach. Coronary arteriography has permitted the recognition of ischemic syndromes which are not due to coronary atherosclerosis. The dynamic nature of these syndromes has widened our thinking on not only the need for but also the approach to angiographic procedures. Finally, rational therapy is best accomplished when we know what we are dealing with.

What are some of the complications caused by arteriography? The most common are local arterial disturbances such as thrombosis, hematoma and the occasional disruption of the artery. The incidence today in a laboratory doing over 200 procedures a year is between 5% and 8%. Ten years ago the problem would have approached 20%. Hypotension is another problem, but the improvement in management of patients with respect to fluid balance and in the nature of the contrast agents themselves have all conspired to reduce the incidence of hypotension. Arrhythmias will always occur, but virtually all of these can usually be managed effectively by either electrical or pharmacologic means. Ideally, catheterization should be postponed if there is digitalis toxicity. Myocardial infarction is a rare complication. The incidence of myocardial infarction has dropped precipitously so that now with better training of those performing the test the risk is about 0.1%. Cerebral vascular accidents will happen, but fortunately these are also rare. The complications related to contrast administration are very infrequent, again, due to improvements in the contrast materials. Finally, mortality from the procedure has been surprisingly low and should be about 0.1%. If a laboratory does not produce statistics in the ranges outlined above, then the practicing cardiologist and internist should question the expertise and the judgment of the operators of that specific laboratory. The referring physician has the right to expect good results from whoever carries out this procedure.

Of great interest is the problem of ischemic heart disease due to syndromes other than coronary atherosclerosis. In recent years, we thought this would be confined primarily to individuals who might have mitral valve prolapse or hypertrophic cardiomyopathy. Both of these entities are usually identified by echocardiography. However, Prinzmetal's variant angina has taken on new significance when it is appreciated that the prevalence of this disorder in one form or another is about 10% of all anginal attacks.

The typical electrocardiographic changes from

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the patient who is undergoing an episode of variant angina is development of S-T segment elevation and then a return of S-T segment to the baseline. There is not much change in the heart rate or blood pressure during these bouts in contrast to increases in hemodynamics with classical Heberden's angina.

Since the work of Maseri, it has come to be appreciated that S-T segment elevation simply means transmural ischemia in ischemic heart disease. In fact, many times S-T segment depression may be seen as is typical for any anginal attack and represents nontransmural or subendocardial ischemia. This brings forth the consideration that many times patients will have variant angina associated only with subendocardial ischemia. This will not be detected unless we know how to identify these patients. They have coronary artery vasospasm or constriction and this must be considered more than formerly. To identify these patients, it is essential to carry out a functional evaluation of the coronary system based on clinical suspicions. The onus is on the angiographer more so in the patient with normal coronary arteries referred because of chest pain than in the patient with abnormal coronary arteries. This requires the input of the cardiologist in those situations where angiography may be performed solely by the radiologist or angiographer without a clinical background or awareness of "variant" history. It may be necessary to document or induce spasm in the patient suspected of having variant angina (Fig. 1).

In the past, one was satisfied to find a patient with a particular chest pain syndrome with normal coronary arteries and quickly dismiss any organic component. Recent work has led us into other areas showing that a certain sizable number of such patients do have something wrong with the heart of an ischemic nature. And, in recent years, it has come to be appreciated that coronary spasm is an example of a form of ischemic heart disease not caused by atherosclerosis. This variety of myocardial ischemia often requires a different type of therapy than might be used in obstructive coronary atherosclerosis.

Certain interventions have been utilized to induce coronary vasospasm in the laboratory. The most effective is the use of graduated small repeated doses of IV Ergonovine. Thirty years ago, Ergonovine was used for the detection of coronary artery disease, but fell into disrepute because the results were not clearly interpretable and some of the responses to the drug were potentially harmful. Considerable experience has now demonstrated that this is the most reliable means of inducing coronary spasm. It is not certain exactly how specific it is for the vasospastic syndrome. Conti and coworkers have compared angiographic findings in patients during an attack of variant angina with results of Ergonovine provocation and shown similarity of response. Vasospasm presenting as occlusive disease of a coronary artery can be reversed with complete return of blood flow following the use of nitroglycerine. Contrariwise, Ergonovine has been used to induce spasm when this is not evident spontaneously. It may sound like a harsh intervention to use, but the recognition of this syndrome in the susceptible patient is so critical it is worth doing. By using nitroglycerine as an antidote there have been no complications in our laboratory. This is especially true when small doses of nitrate are given directly down the coronary artery after spasm occurs.

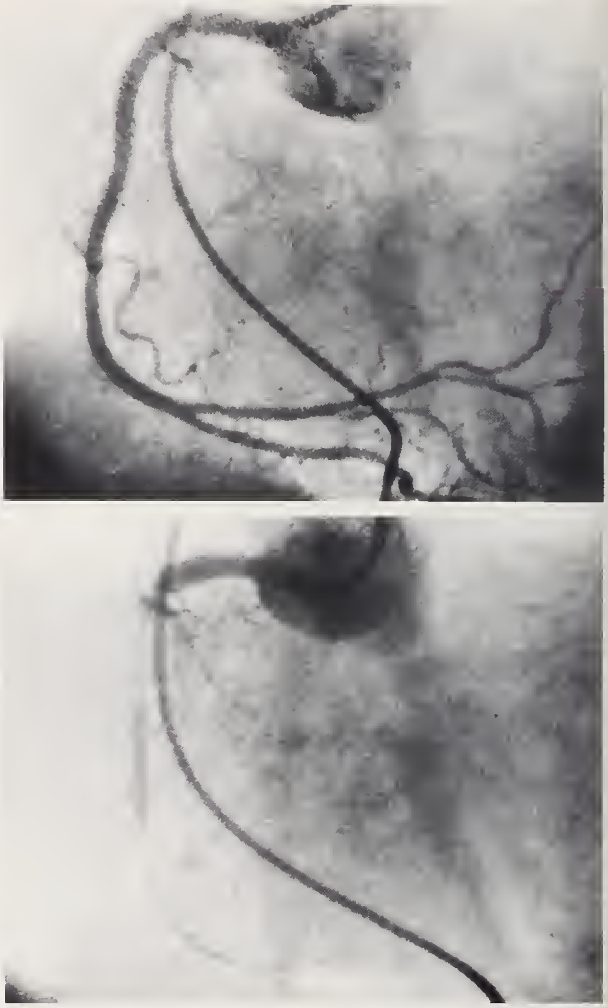

FIG. 1. Right coronary arteriogram (LAO projection). A. Normal. B. Diffuse vasospasm. (Courtesy of Dr. Augusto Pichard).

There are certain rare situations in which it might be very important actually to measure coronary blood flow. If one is concerned about angina pectoris in an individual who has ventricular hypertrophy it may be very important to know what the coronary blood flow is and what reserve coronary flow capacity this system has. Preliminary reports also suggest some patients have low coronary reserve, angina and no hypertrophy or organic coronary disease. Can one determine if loss of coronary reserve is a basis for clinical ischemic symptoms? This hypothesis is now beginning to be tested as one of the criteria for deciding when hypertrophy in certain diseases such as aortic stenosis begins to outstrip the available blood supply and becomes a reason in and of itself to consider therapy directed at the primary disease, that is, aortic valve replacement.

The quantification of arterial lesions and the relationship to selective perfusion deficits are still major problems and may call for selective testing when uncertainty about the significance of a given coronary lesion exists (Fig. 2). For example, when a 50% lesion of a right coronary artery is demonstrated, should this be considered a cause of the patient's chest pain? Answers to this question may come from studying provoked regional perfusion deficits or from a careful quantitative analysis of the obstruction itself. The point is that there has to be a much more critical look at coronary lesions that are not obviously severely obstructive because they may or may not be adequate to explain what is going on in a particular patient. Standard coronary angiograms demonstrating borderline stenoses do not always explain everything and spasm alone or in combination with a fixed obstruction may play a role.

Another syndrome that is much less common but deserves some attention is systolic compression of the coronary artery by a myocardial bridge. There have been reports of patients who develop myocardial ischemia, usually in the distribution of the left anterior descending coronary artery, who have normal arteries but a recognizable systolic compression by overlying myocardium. In previous years, this particular finding has been ignored since most flow is believed to occur in diastole and compression in systole was considered a curiosity that had no significance. This has been questioned in recent years and some surgeons have been brave enough to operate on patients who have demonstrated this phenomenon. With further experience using intervention testing to determine if a segmental perfusion deficit can be demonstrated under stressful conditions, it may be that in selected patients release of a myocardial bridge may be appropriate.

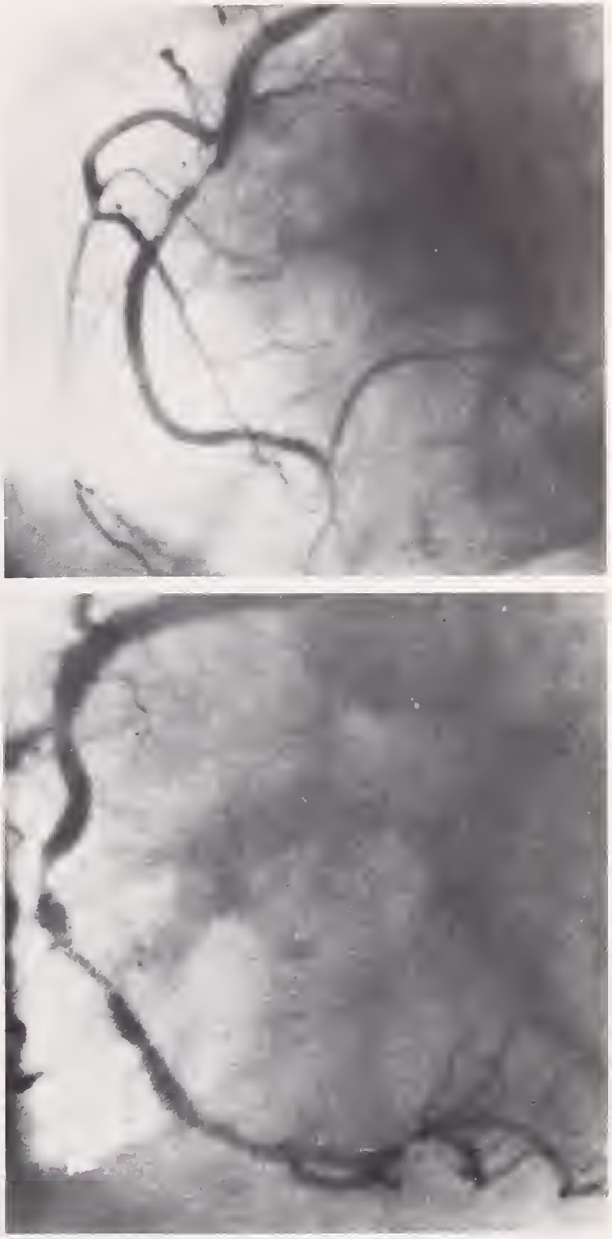

FIG. 2. A. Right coronary artery (LAO projection). Mid-vessel obstruction with good distal caliber. B. Right coronary artery (LAO projection). Multiple diffuse obstructions throughout the artery.

Ventricular performance can be evaluated by means of radioisotopic techniques. There are occasions, however, when contrast ventriculography may be necessary, particularly if surgery is being considered. It is true that a search for diffuse versus localized abnormalities of contraction can be well done with a noninvasive technique. It is not always possible to be totally confident of findings of such tests, particularly if surgery hangs in the balance and contrast ventriculography becomes as essential as defining the specific coronary lesions (Fig. 3).

Diagnostic uncertainty begins with symptoms of uncertain etiology. This is particularly true

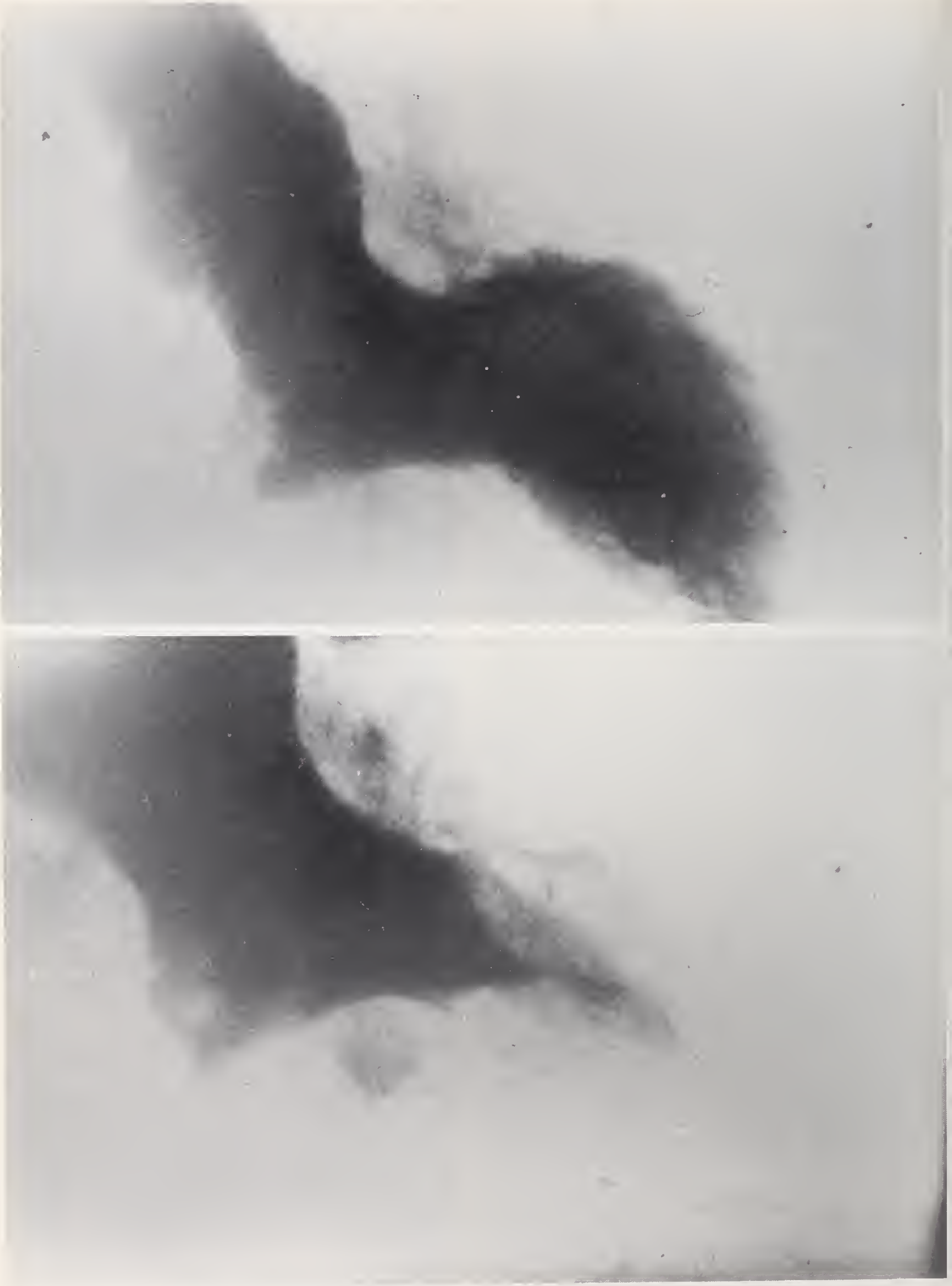

Fig. 3. Left ventriculogram (RAO projection of endsystolic image). A. Note persistent apical bulge simulating aneurysm and excellent basilar contraction. B. Following nitroglycerine contraction improves so that there is uniform excellent emptying. The "aneurysm" of frame A is obviously functional and improved with nitroglycerine improving either local blood flow or hemodynamic loading conditions. (Courtesy of Dr. Augusto Pichard)

with chest pain syndromes. It is important to appreciate that the classification of typical angina pectoris versus atypical angina no longer holds the weight that it might have been given in the past. Even if pain is far from typical, there is a reasonable chance that an individual could have ischemic heart disease. There is also the possibility that this may represent variant angina in which there is a vasospastic component to the ischemia and pain.

Occasionally, there is the possibility of two diagnoses existing in the same patient, and it becomes essential in guiding some phases of therapy, particularly when early therapy has not given satisfactory results. For example, the individual may have hypertrophic cardiomyopathy with the diagnosis made by echocardiography. The patient, however, has angina pectoris and happens to be in a high prevalence group, that is, 60-year-old male with certain risk factors and an abnormal electrocardiogram. In this situation coronary angiography may be necessary to clarify the problem and to allow for proper therapy.

Catheterization is important in some patients with heart failure or with poorly understood tachyarrhythmias when the exact etiologic diagnosis is not obvious.

A problem that occasionally arises is the individual who has no symptoms but has had certain abnormal noninvasive tests. An abnormal rest electrocardiogram or stress electrocardiogram or abnormal radionuclide perfusion image in the asymptomatic individual might prompt invasive study. This is particularly cogent in the asymptomatic airline pilot with an abnormal stress electrocardiogram whose entire career may be in jeopardy on the basis of this abnormal test.

There are certain patients who have abnormal perfusion images and yet who have perfectly normal coronary arteries. Do these individuals have heart disease? Do we know that they have normal coronary arteries until we find out? In a small subset of individuals it may be important to do angiography because of the particular noninvasive test done or because of some sensitive occupation or other personal issue requiring exact diagnosis.

The management of the asymptomatic patient always remains a dilemma. One may never be sure what is the right thing to do. Part of this is

TABLE I

Indications for Catheterization/Angiography in Ischemic Heart Disease

Chronic Stages

- I. Diagnostic Uncertainty
  - A. Symptoms of Uncertain Etiology
    - 1. Pain: classical versus atypical
      - a. Coronary artery disease
      - b. Variant angina
      - c. Mitral valve prolapse
      - d. Idiopathic hypertrophic subaortic stenosis
      - e. Other
    - 2. Congestive heart failure
    - 3. Tachyarrhythmia
  - B. No Symptoms but Certain Tests Abnormal
    - 1. Electrocardiogram
    - 2. Perfusion imaging
    - 3. Significant precocious or familial hyperlipidemia
- II. Diagnostic Certainty but State and Stage of Disease Unknown and Unquantified
  - A. Prognosis and Therapy
    - 1. Angina pectoris
    - 2. Status post myocardial infarction
- III. Diagnostic Uncertainty in Detection of Coronary Artery Disease in Presence of Other Forms of Heart Disease
- IV. Improve management
  - A. Medical Therapy: Different therapy for coronary artery disease and vasospasm
  - B. Surgical Therapy: Planning and suitability
  - C. Evaluation of Therapy

Acute Stages

- I. Unstable Angina or Intermediate Syndrome
  - A. Stabilize Patient First: Beta blockers, nitrites, etc.
  - B. Study as Much for Diagnosis as Therapy: i.e., variant angina
- II. Acute Myocardial Infarction
  - A. Certain Patients With Shock and Failure
    - 1. Spasm
    - 2. Occlusion: ?Angioplasty ?Thrombolysis

based on uncertainty over what is to be done with the information once it is obtained. Therefore, in dealing with this category of patients, the question should be asked whether the information obtained from the angiographic procedure will change the management of the patient and will it help the patient. If the answer is equivocal, then the procedure should not be done. But taking the airline pilot as an example, that individual is offered a great service if the abnormal noninvasive test is clarified.

Most of the time angiography is used when the diagnosis is not in doubt but rather when the problem is definition of the state and stage and degree of the disease. In this regard the questions of prognosis and therapy are the major concern. Part of this depends on one's philosophy. Are you going to carry out exercise stress testing? Are you going to do perfusion imaging or angiography by radionuclide means? What will you do with the information and how will it affect the decision?

Part of the response here depends upon what is learned from these other procedures. For example, if you do an exercise electrocardiogram and from this test you find severe S-T segment depression and if in addition it occurs at a low level of exercise, and if the patient presents with chest discomfort, unique dyspnea, unexpected diaphoresis or blood pressure that did not rise as expected, then a great deal has been learned from that noninvasive test. This should guide the physician to question that patient's prognosis very seriously and want to know about the coronary arteries. The management program in such a patient should meet the highest criteria. If warning signs about prognosis emerge from noninvasive procedures, then we want to quantify the amount and type of vessel disease and ventricular function and give serious thought to whether current therapy is adequate.

The same approach applies to patients after myocardial infarction. We want to know what the blood vessels look like in somebody who has had a myocardial infarction, particularly if he/she is below the age of 50. I would be guided by any of the criteria that would indicate the true prognosis. I probably would avoid the procedure if a radionuclide angiogram showed a very low ejection fraction and a diffuse, poorly contracting heart. In such a situation, we need no coronary angiogram because management of the patient will change very little. So again, this is when screening helps but one may not find this information all the time. We wish to know if there is extensive vessel disease and other unrecognized old infarcts. In order to commit a patient to appropriate and full medical therapy we need the maximum knowledge about his coronary vessels and ventricular function.

Probably the greatest reason we do angiography is to improve how we manage our patients. Many times we have treated patients for typical angina and find that the treatment does not work. How does one react when the patient does not respond to beta blockade? For example, you achieve blockade by whatever dose of blocker is required and the patient continues to have attacks of angina. In the past we tended to say that this would mean the patient did not have atherosclerotic angina. We have almost got a diagnosis on the basis of lack of response. Well, there are two points: 1) the lack of response might mean there may be such severe three-vessel or left main coronary disease that no medical therapy is going to get this patient comfortable; or 2) the diagnosis is wrong, but it is not necessarily the absence of heart disease but different heart disease. We have seen a number of individuals in whom beta blockers have not been effective and the reason has been that the patient has vasospastic or variant angina and therapy is not achieved by beta blockade but rather with nitrites or some of the calcium antagonist drugs acting as arterial smooth muscle dilators.

While one probably knows about left ventricular function by radionuclide angiogram, one does not necessarily know what the blood vessels are like. It is very important to understand that there are coronary vessels which are bypassable and others which are not. In our own experience at Mount Sinai we have looked at mortality and morbidity. When a surgeon bypasses vessels that have poor runoff or major distal atherosclerosis, such patients sustain myocardial infarctions during the follow-up period more frequently than those with good runoff. There are situations in which distal disease precludes surgical consideration. So, early on in certain patients you may want to know if coronary bypass is even an option for therapy. This will guide you in selecting the level of intensity of medical therapy because that may be the only therapeutic route available.

Now, the last comments concern the acute syndromes of coronary disease. In unstable angina or the intermediate coronary syndromes is there a need to rush that patient into angiography? Usually not. It is best to stabilize this individual with the use of beta blockers and nitrates. These are effective in most individuals. Occasionally, we need to go on to management with other agents or with balloon counterpulsation. Generally speaking this will be effective. Angiographic studies should be done during that hospitalization, as much for diagnosis as for therapy, because some of these individuals will have variant angina and the treatment which will be used in the followup period will be very different from that which will be used for ordinary atherosclerosis.

In patients who have acute myocardial infarction with shock or failure, how often is catheterization needed? In this situation radionuclide angiography has been especially helpful in the desperately ill patient and provides us with early information as to whether a hypodynamic, barely contracting ventricle in the face of shock precludes any major attempt at salvage. There are rare situations, such as rupture of septum or papillary muscle, in which the noninvasive clues provide reason to do a catheterization which is then done with the expectation that surgical repair is imminent.

One of the more interesting recent therapies is that of early correction of acute coronary obstruction. Oliva has demonstrated that in patients who have an acute myocardial infarction a certain percentage exhibit coronary arterial spasm, and while the proof is far from conclusive, the suggestion has been made that perhaps relief of that spasm may play a role in limiting myocardial infarction size. There also is a recent wave of interest in transluminal coronary angioplasty and *in situ* thrombolysis, the latter in acute myocardial infarction.

Summary

Recent advances in noninvasive means for imaging the heart have still not achieved the accuracy and clarity of definition possible with coronary catheterization and angiography. Catheterization techniques are particularly useful in distinguishing the extent to which vasospasm, ventricular hypertrophy, systolic compression of atherosclerotic lesions may be responsible for ischemic pain. Contrast ventriculography is still the most accurate means of evaluating ventricular performance. When a patient is asymptomatic but has abnormal noninvasive tests, angiography may help to determine the cause of the ischemia. The main consideration in submitting patients to catheterization is whether the information obtained through angiography will help the patient. The greatest reason for carrying out angiography is to improve patient management. Insofar as these procedures assist in clarifying our knowledge of the etiology and extent of disease, they assist in the refinement of diagnosis and in prescribing a therapeutic regimen.

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Ischemia of the Colon

Richard H. Marshak, M.D., Arthur E. Lindner, M.D.,* and Daniel Maklansky, M.D.

Vascular occlusion of any segment of the colon usually causes the sudden onset of abdominal pain associated with passage of blood from the rectum. The episode may vary in severity from a catastrophe of bowel gangrene to an incident so mild that the event is recalled only in retrospect, sometimes after roentgen examination discloses a lesion.

The phrase "ischemic colitis" has been used to designate the changes that occur in the colon after vascular occlusion (1). Perhaps a better phrase would be "ischemia of the colon," because on pathologic examination, there is little evidence of an inflammatory reaction in the early stages of this condition (2). The most common locations for ischemia are the splenic flexure, representing bowel supplied at the junction of the superior and inferior mesenteric arteries, the rectosigmoid, and the cecum. Any segment of the colon may be implicated, however, including the rectum.

The effects of vascular occlusion depend on the rapidity of onset, the length involved, the efficiency of the collateral circulation, and the presence of associated diseases. Rapid occlusion of a major vessel results in massive tissue necrosis, peritonitis, and shock. Such desperate events allow little opportunity for contrast radiographic study. When the insult involves segmental rather than trunk vessels, however, or when a closure is slow and collateral flow can provide an adequate blood supply, total infarction of bowel may not occur. In this circumstance, complete healing may follow.

Often, an intermediate situation results in which blood flow is minimally sufficient and does not cause death of the intestine, yet is inadequate for complete recovery of the damaged wall. Such partial recovery may produce radiographic features that resemble inflammatory bowel disease or tumor and must be distinguished from these entities.

The etiology of ischemic disease of the colon may conveniently be considered in terms of large artery occlusion and the "nonocclusive states" (3).

Large artery occlusion is usually caused by arteriosclerosis, with narrowing of the superior mesenteric artery involving the right side of the colon, or of the inferior mesenteric artery involving the left side. It may result from damage to the inferior mesenteric artery supply during abdominal aorta surgery, such as removal of an aneurysm. Embolism may occur in the superior mesenteric artery, but is less likely in the inferior mesenteric artery, which arises more obliquely from the aorta.

With the development of angiography and early surgery in the management of ischemic bowel disease, it became apparent that no large vessel closure could be demonstrated in a large propor-

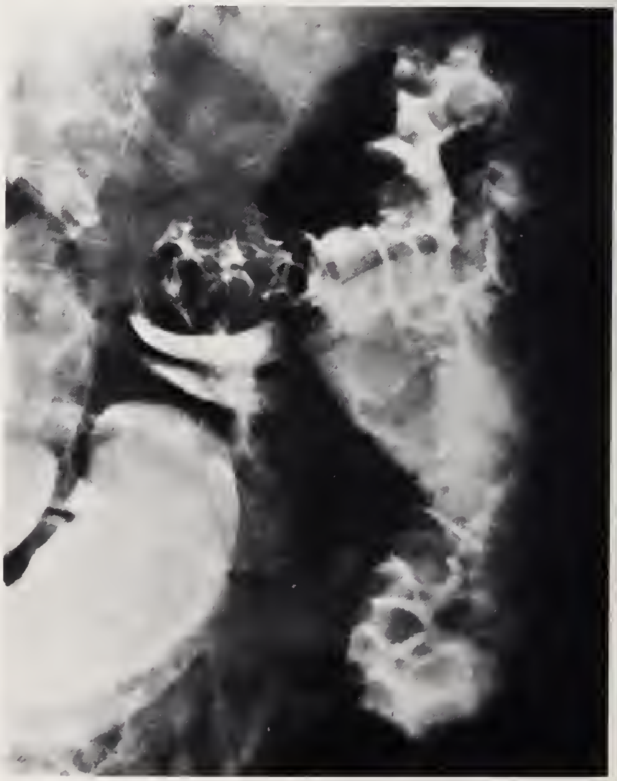

Fig. 1. Ischemia of the colon. The proximal descending colon and distal tranverse colon demonstrate multiple indentures along the contour of the bowel, resulting in a scalloped appearance or thumbprinting.

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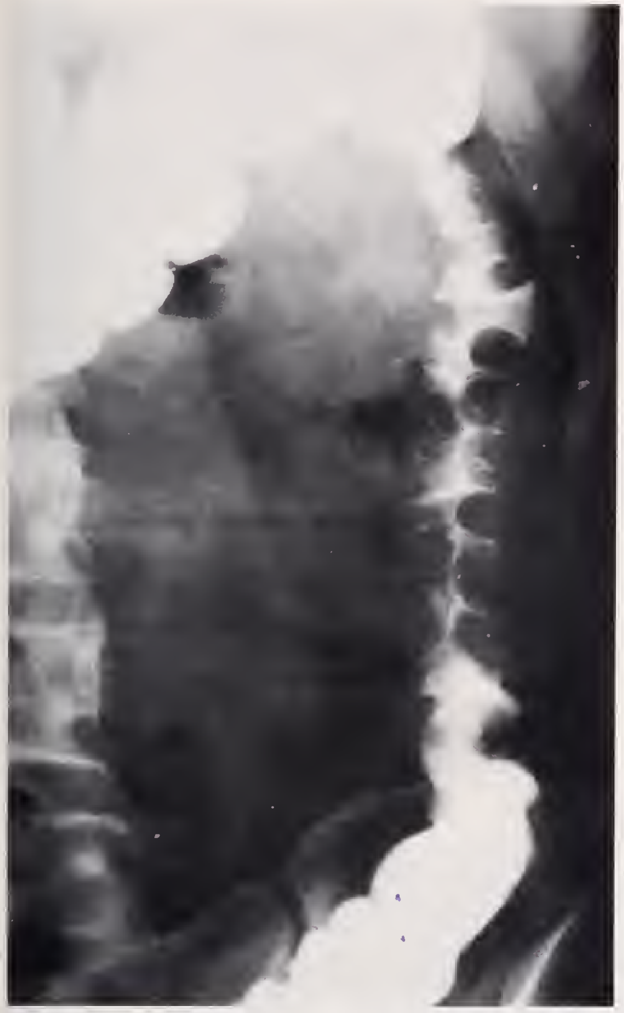


FIG. 2. Ischemia of the colon in another patient. Scalloping or thumbprinting is seen in the descending colon.

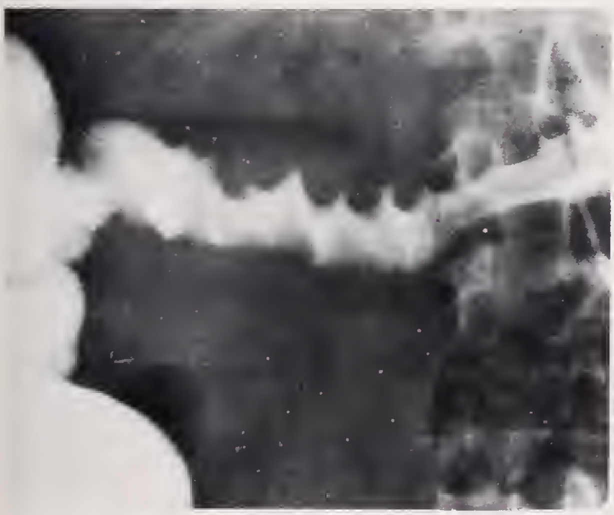
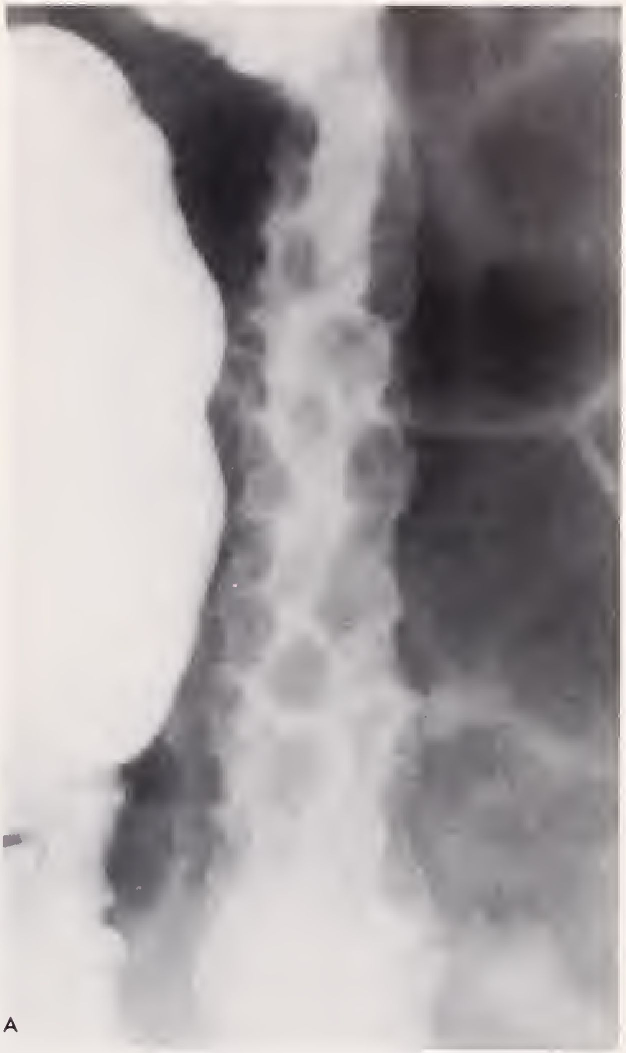


FIG. 3. Ischemia of the colon. A spot film of transverse colon reveals narrowing, rigidity, and thumbprinting. The patient is an elderly female who presented with severe abdominal pain and rectal bleeding. This examination was performed one week after the acute episode. A repeat barium enema one month later was normal.



A

FIG. 4A. Ischemia of the colon. Magnified view of segment of descending colon involved with ischemia. Multiple scalloped and thumbprinting areas are identified. When seen en face, these thumbprints simulate polypoid filling defects.

tion of patients. This phenomenon has been termed "nonocclusive ischemia" and probably represents a group of conditions having in common a perfusion defect within the wall of the bowel (4). Associated conditions in patients with nonocclusive ischemia include congestive heart failure, digitalis toxicity, hypotension, vasculitis, vasospasm, hyperviscosity syndromes, and bowel distention.

Pathology

The pathologic features of vascular occlusion of the bowel have been well described (2, 5). The layers of a segment of bowel are not equally sensitive to impairment of their blood supply. The mucosa and submucosa are most dependent on intact blood flow. Colonic mucosa is less sensitive to ischemia than is small intestinal mucosa (6).

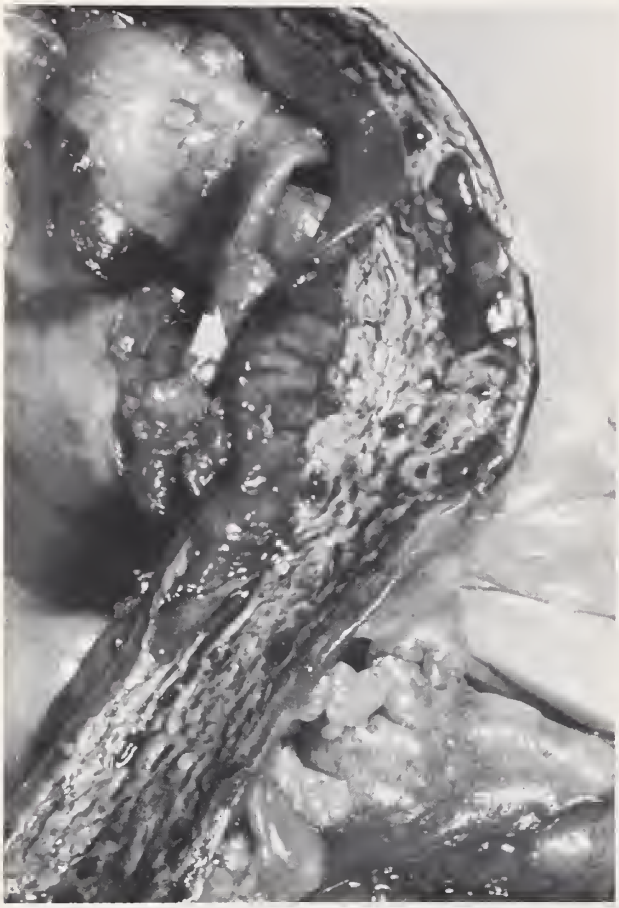


FIG. 4B. Specimen of patient in 4A. Areas of submucosal edema and hemorrhage are identified. These congested areas of mucosa and submucosa cause the scalloping and thumbprinting described in previous studies.

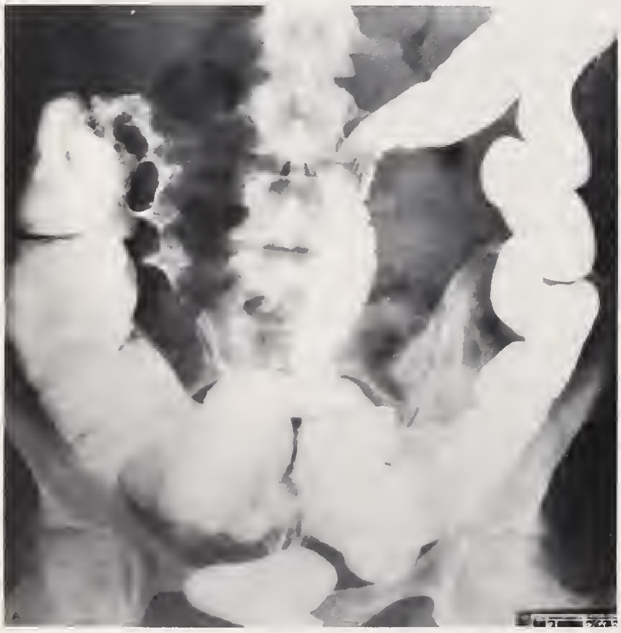


FIG. 5A. Ischemia of the colon. Marked spasm and irritability of the transverse colon associated with thumbprinting. The lesion extends for a distance of approximately eight inches in a redundant transverse colon.

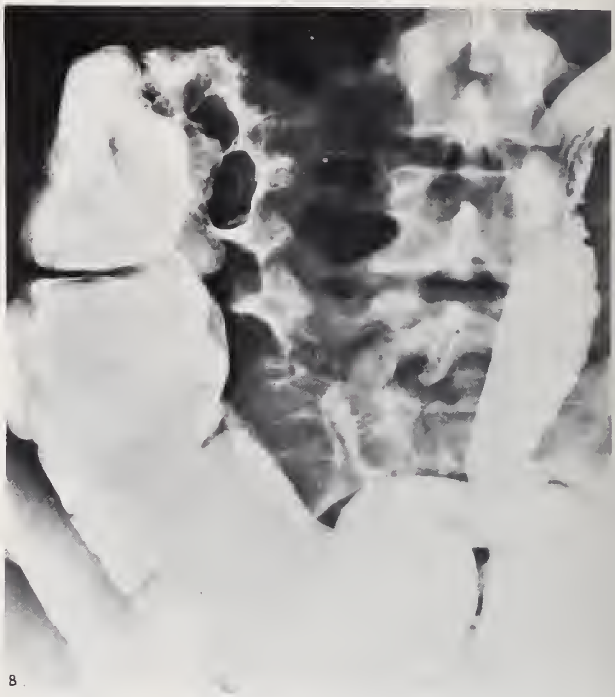


FIG. 5B. Magnified view of 5A.

The initial changes in vascular occlusion are edema, hemorrhage, and ulceration. The ulcers subsequently may heal, perforate, or produce stricture. Submucosal hemorrhage and edema

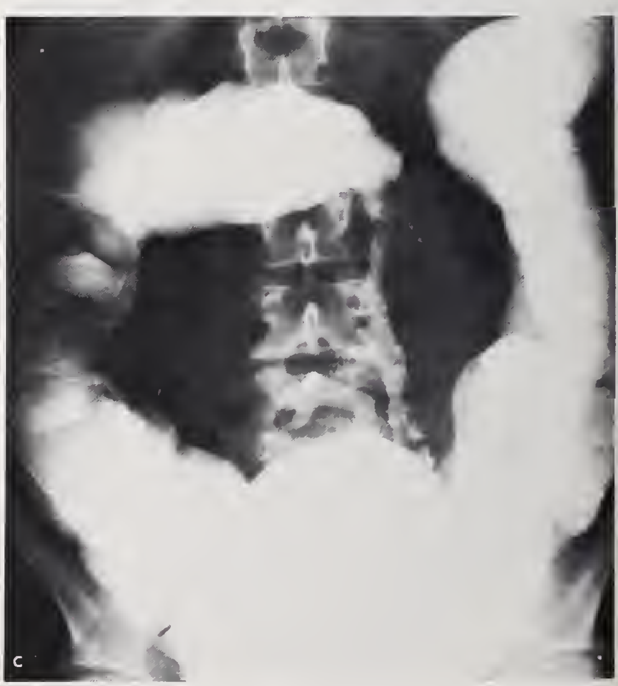


FIG. 5C. Ischemia of the colon. Same patient as 5A. Repeat barium enema examination performed one month later reveals a moderate degree of narrowing associated with moderate pseudosacculation. The mucosa in the involved area is effaced. No discrete ulcerations are identified. Increased secretions are noted.

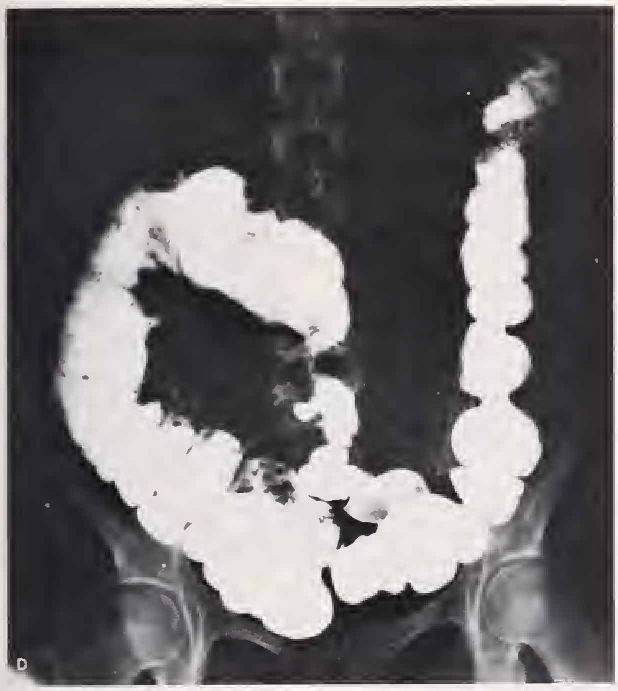


FIG. 5D. Ischemia of the colon. Same patient as 5A, one month later. There is now a stricture at the site of involvement. Multiple pseudodiverticula are identified.

cause localized nodularity or diffuse thickening of the mucosal folds. Ileus develops, either local or diffuse, and fluid accumulates within the lumen of the damaged gut. After the vascular injury, recovery may be complete, because intramural blood and edema are resorbed and the ulcerations may heal without scarring. On the other hand, fibrosis may advance to permanent stricture and proximal dilatation.

On gross examination, transmural infarction is seen in the most severe or gangrenous disease, with involvement of the serosal surface. In less severe ischemia, patchy mucosal ulcerations, hyperemia, and edema are present, with marked submucosal edema. It is this submucosal edema that accounts for the "thumbprinting" seen on barium enema examination.

A sequence of changes can be demonstrated on histologic examination. Focal coagulation necrosis occurs in the lamina propria, with congestion of the microcirculation and extravasation of blood. As the process continues, deeper portions of mucosa are involved, then the submucosa, and later the muscular layers. Inflammatory changes

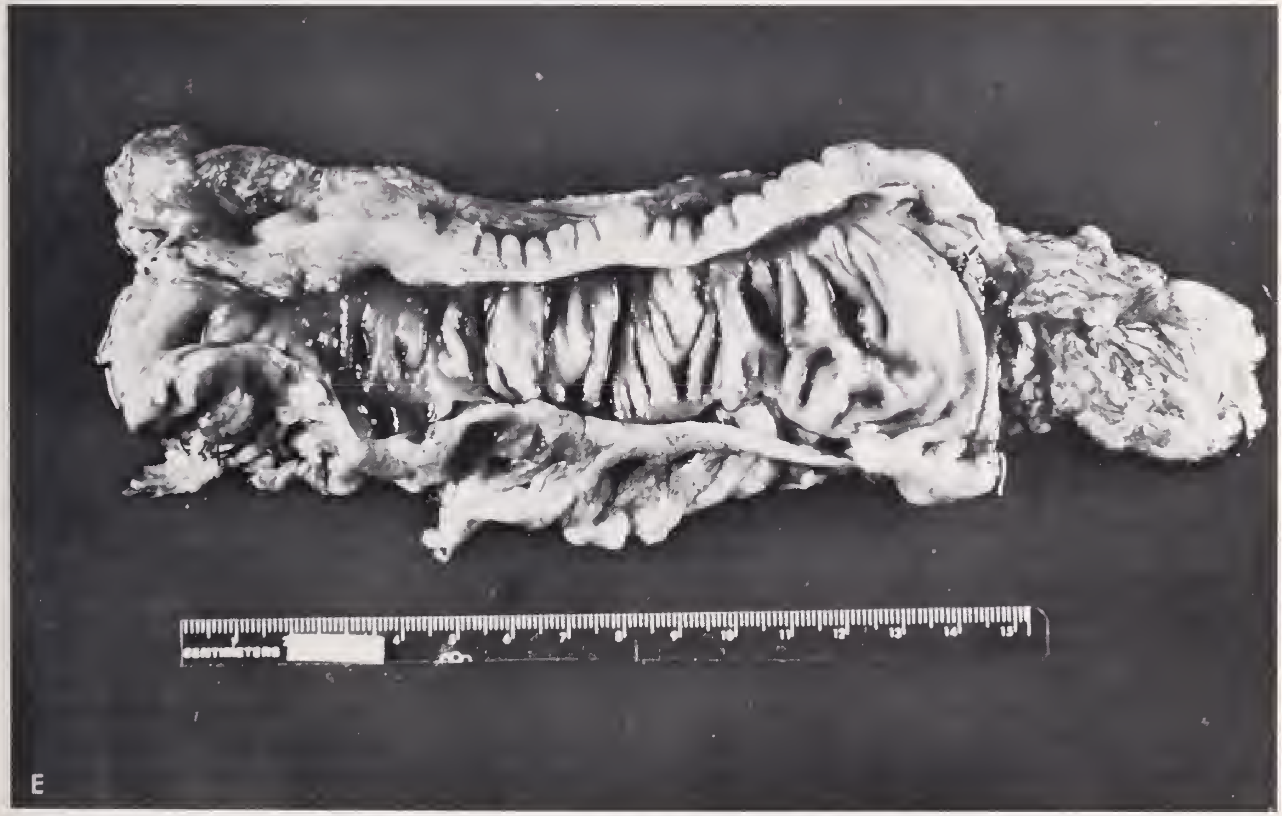


FIG. 5E. Ischemia of the colon. Same patient as 5A. Surgical specimen of the stricture in the midtransverse colon described in 5A, B, C, and D. Note the multiple orifices of the pseudodiverticula. This sequence occurred in a 28-year-old female who was taking birth control pills.

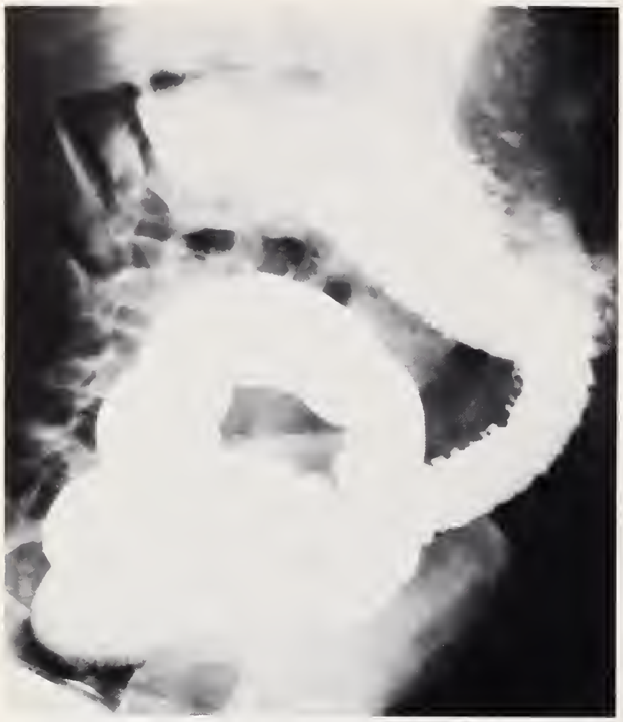


Fig. 6. Ischemia of the colon. Barium enema examination performed one week after onset of acute abdominal pain and rectal bleeding in a 72-year-old male. Multiple ulcerations are identified on the mesial border of the descending colon. In some areas the ulcers have a collarbutton appearance.

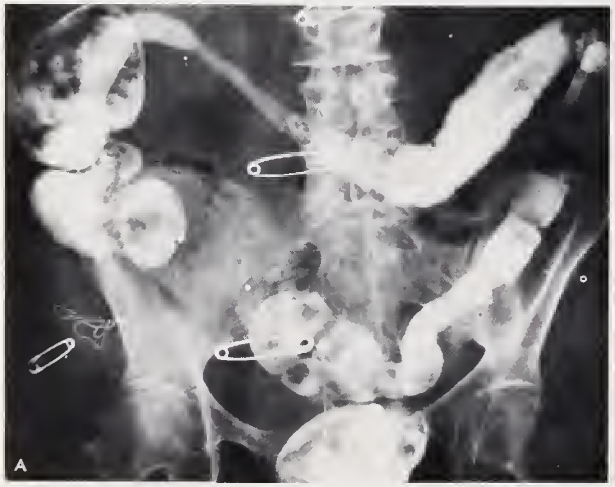


Fig. 7A. Ischemia of the colon. Barium enema examination one month after an acute episode of rectal bleeding and abdominal pain reveals narrowing and limitation of distensibility of the proximal transverse colon, with a loss of mucosal pattern. Thumbprinting is no longer seen. Pseudosacculation has not yet occurred.

now take place, with coagulation necrosis, cryptitis, and formation of a pseudomembrane composed of necrotic mucosa, acute inflammatory cells, fibrin, and bacteria. Thus, the immediate effect of acute ischemia is necrosis of tissue. Secondarily, there is infection with organisms that invade the necrotic tissue of the bowel wall.

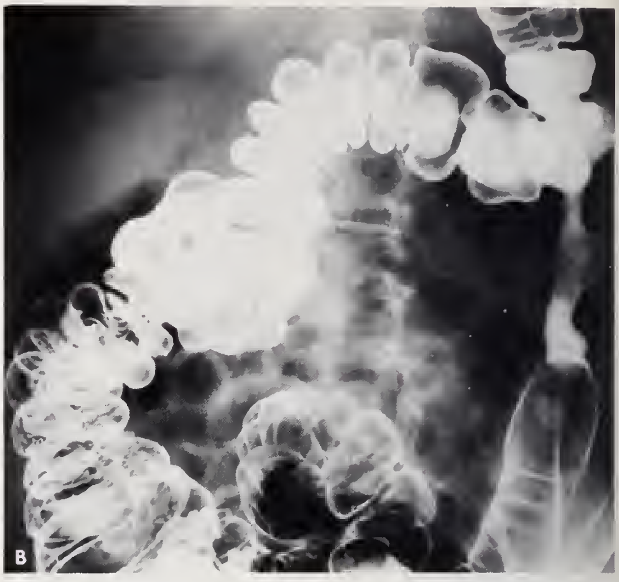


Fig. 7B. Ischemia of the colon. Localized segment of narrowing in the proximal descending colon, with smooth contours and loss of the mucosal pattern. A single sacculation is identified. The narrowing indicates early stricture formation.

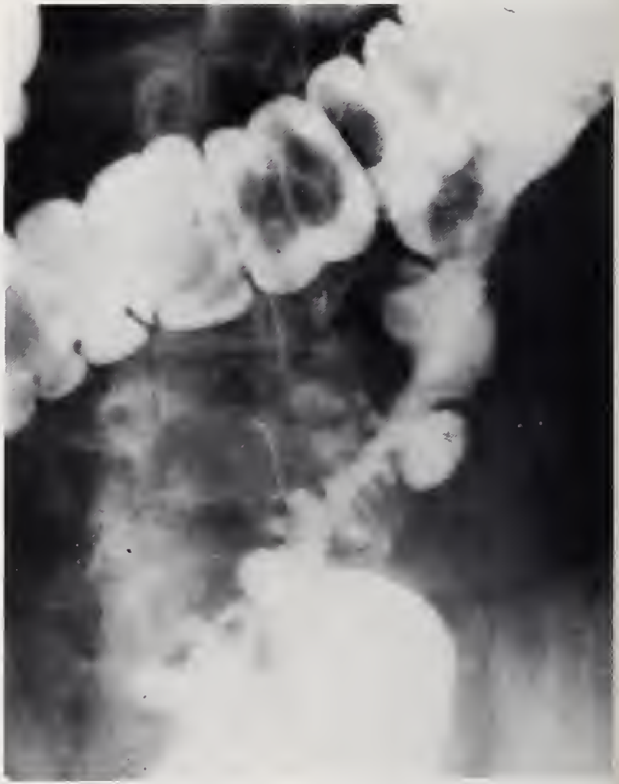


Fig. 8. Ischemia of the colon. Late stage. Narrowing and rigidity of the descending colon are revealed, as well as multiple sacculations or pseudodiverticulae at this site.

When strictures form, marked fibrosis of the submucosa and muscular layers is present. The mucosa is ulcerated and replaced by granulation tissue. At the edges of the ulcerated areas, epithelial regeneration may be seen.

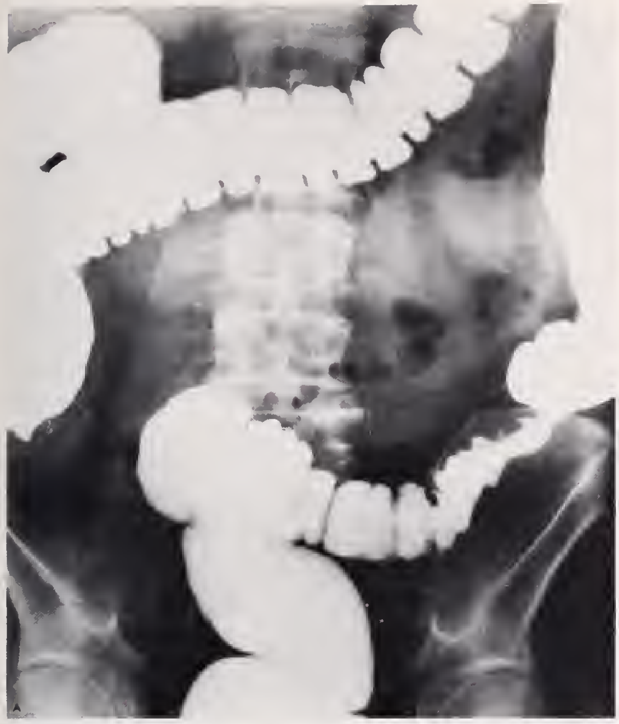


FIG. 9A. Ischemia of the colon. Late sequelae. Barium enema examination obtained two years after an initial ischemic episode reveals an area of eccentric stricture in the distal descending colon associated with pseudodiverticula formation.

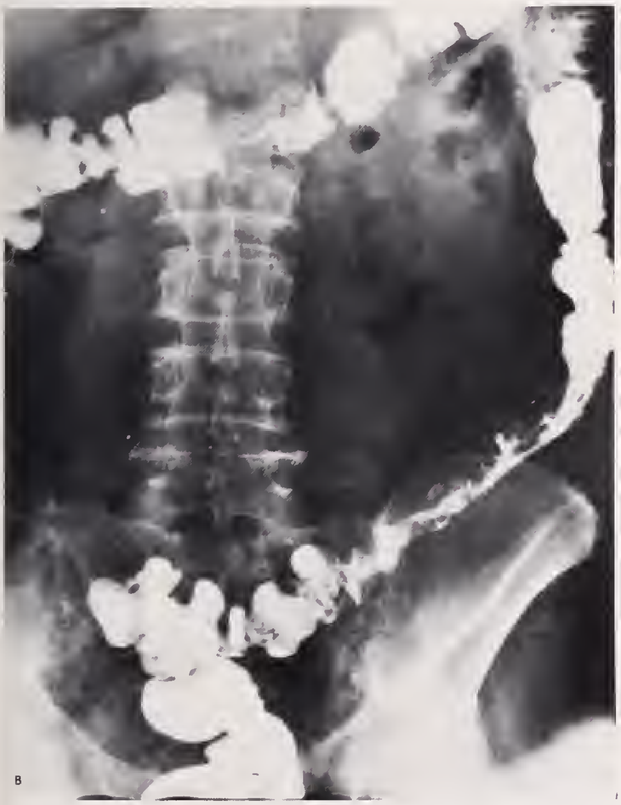


FIG. 9B. Same case as 9A. Postevacuation film. After evacuation the multiple pseudosacculations are identified. The stricture is less marked.

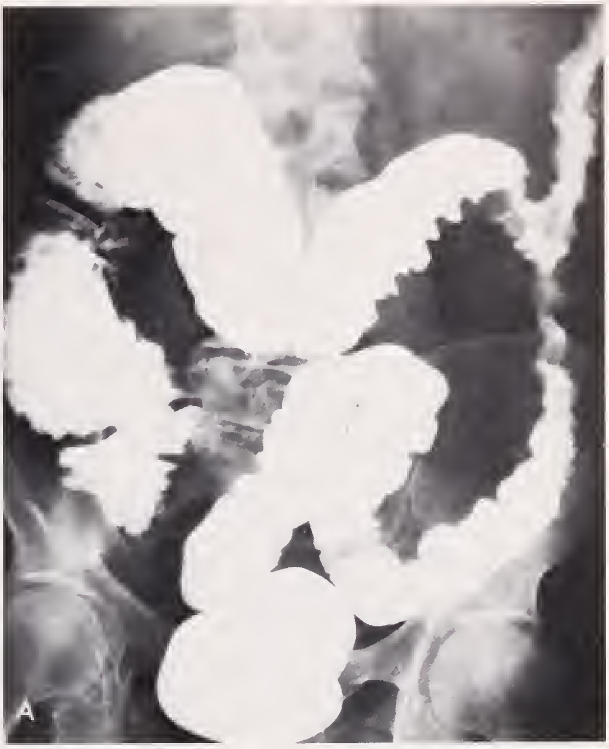


FIG. 10A. Ischemia of the colon. This 67-year-old male had sustained a coronary occlusion four years previously. There is a moderate degree of spasm and rigidity of the distal transverse and descending colon. The folds are thickened in association with scalloping of the contours. No discrete ulcerations are identified.

Roentgen Features

A preliminary film of the abdomen may reveal slight distention of a portion of the colon. Dilatation has been reported in acute ischemic disease, and the appearance may be like that seen in ulcerative colitis, with considerable distention of the colon, areas of necrosis, and pseudopolyp formation. When both the small bowel and the colon are involved, the small bowel may become dilated, with edema and thickening of the valvulae conniventes. As the episode advances, the haustra become thickened and edematous, and the colon contains a large number of secretions. With further edema, the haustral markings disappear completely. Localized perforations may be identified as pneumatosis coli. These occur in areas of more marked disease, which the pathologists interpret as localized gangrene of the bowel.

Barium enema examination during the acute stages of vascular injury demonstrates spasm as well as thickening and blunting of the mucosal folds. Multiple indentures that have been termed "scalloping" or "thumbprinting" are seen along the contours of the bowel (Figs. 1–3). When seen face-on, these thumbprints appear as polypoid filling defects (Fig. 4). Increased intraluminal

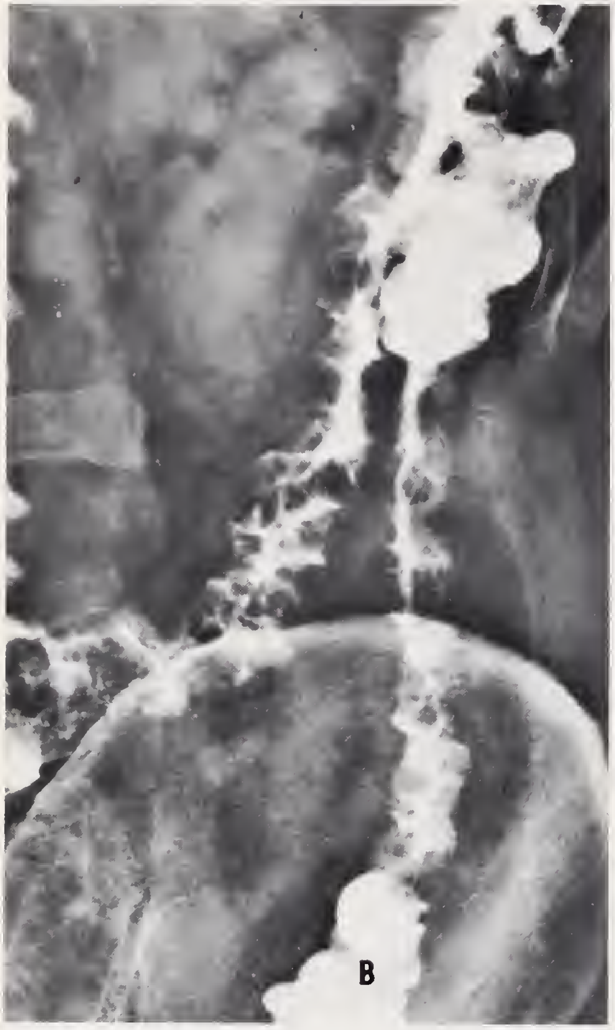


FIG. 10B. Evacuation film demonstrates findings shown in 10A.

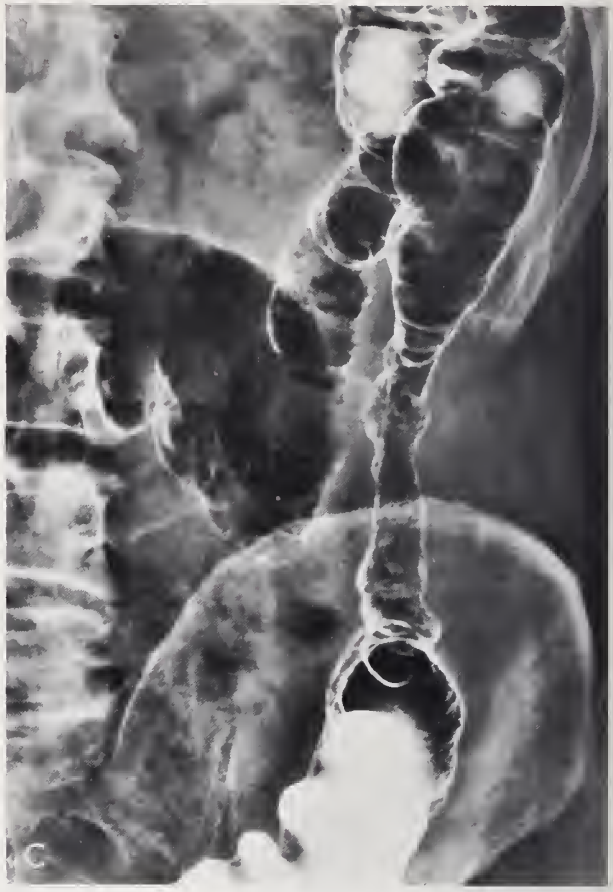


FIG. 10C. Ischemia of the colon. Same patient as 10A, one month after the original examination. In the mid-descending colon there is a narrowed segment of bowel approximately five inches long, with smooth contours.

secretions are present. As edema progresses, the folds become more thickened and hazy (Fig. 5A). Although ulcerations are seen in specimens of bowel resected during this stage, they are not always deep enough to be recognized radiographically within the edematous, fluid-filled bowel as individual ulcers, even with air contrast studies. With diffuse ulceration, the mucosa may be completely effaced. In some cases, ulceration is so extensive that sarcoma is simulated. Collarbutton ulcers, as seen in inflammatory bowel disease, have also been recognized (Fig. 6).

After the initial thumbprints disappear, the involved colon often has the appearance of a segmental colitis with loss of mucosal integrity (Figs. 5C, 7). The ulcers that result may be fine and superficial. Then, with extension of the ulcerative process, they burrow submucosally and laterally for a short distance to give the collarbutton appearance (Fig. 6).

As healing and fibrosis progress, flattening and rigidity of one wall tends to develop. The antimesenteric border becomes pleated, forming multiple sacculations or pseudodiverticula (Figs. 7B, 8, 9). With continuing fibrosis, a long tubular segment with smooth contours and a concentric lumen is identified (Fig. 10), and finally a stricture with proximal dilatation is seen (Fig. 5D and E). Stricture of the rectum rarely occurs, probably because collateral blood supply to the rectum is excellent.

When a stricture develops, it is usually shorter than the original length of ischemic involvement seen radiologically. This suggests that at the onset there was probably more widespread involvement of the blood supply.

Sinus tracts and fistulas are unusual in ischemic disease, probably because ulcerations tend not to be deep.

The sequence of these radiographic findings is rapid and in a period of several weeks the lesion may progress from the initial stage of spasm and edema to stricture formation. In the stages before extensive fibrosis develops, partial or complete reversibility may occur (Figs. 11–13). The ischemic process may stop at any one of the stages

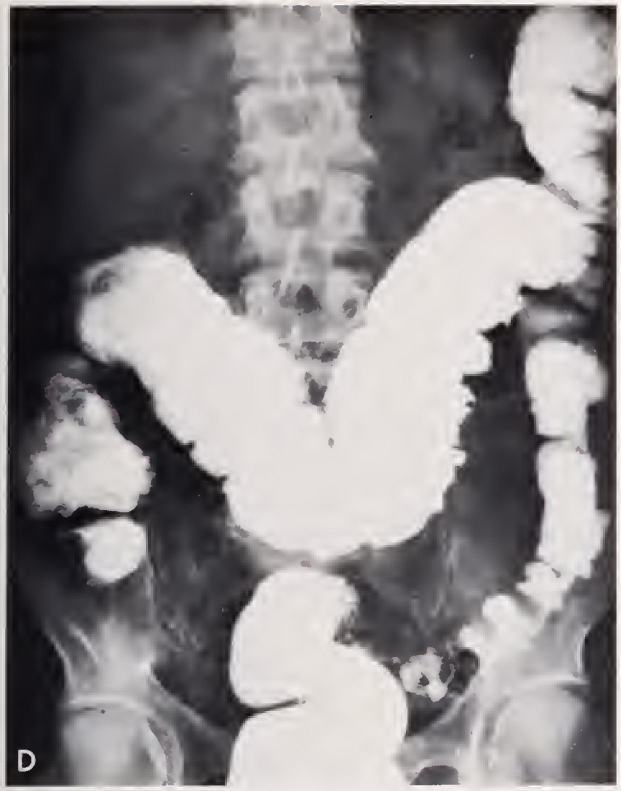


FIG. 10D. Same patient as 10A, two months after the original episode. Moderate reversibility of the lesion is demonstrated. At this time, there is slight flattening of the inferior wall of the distal transverse colon. The descending colon reveals sacculations and a moderate number of diverticula.

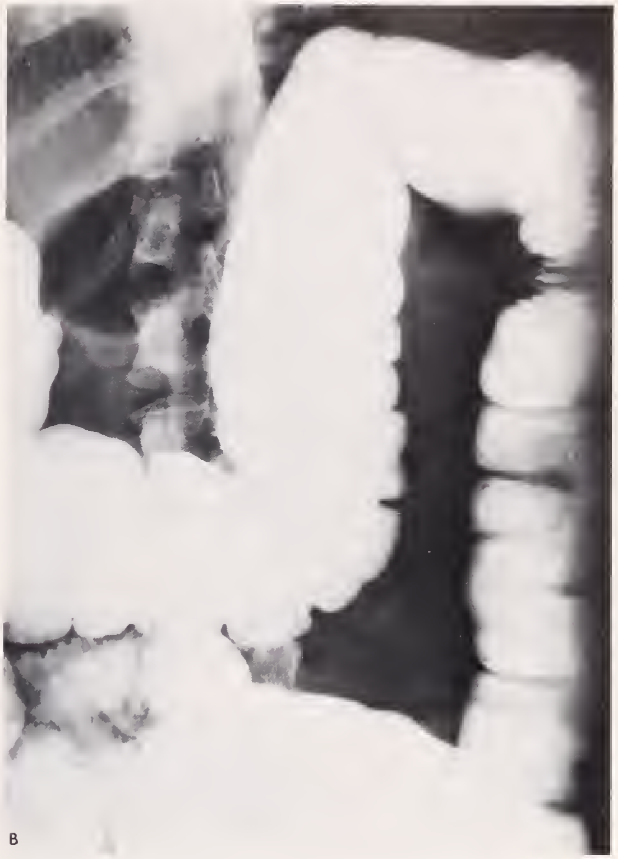


FIG. 11B. Same patient as 11A. One month later there has been almost complete reversibility. Only minimal flattening remains.

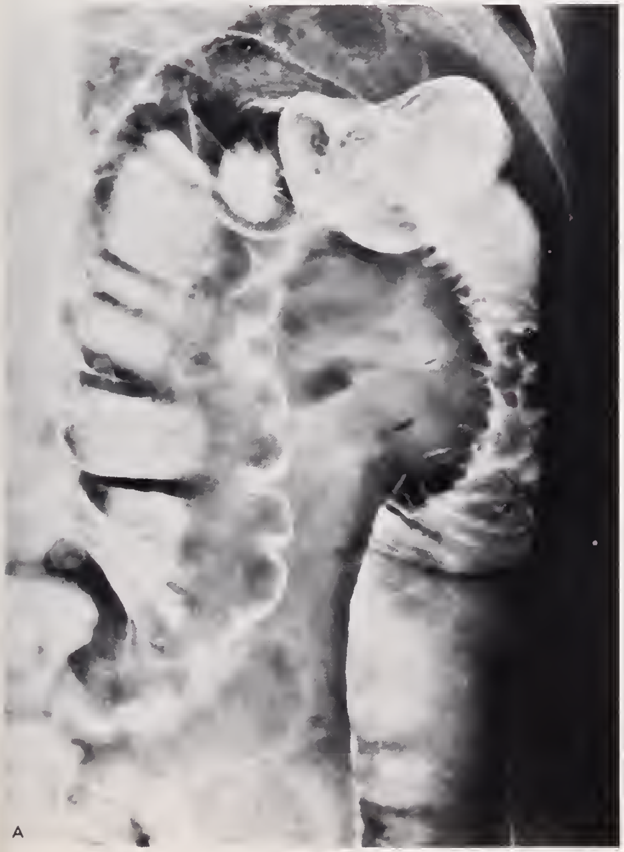


FIG. 11A. Ischemia of the proximal descending colon.

previously described, and the patient may first be seen at any stage.

Ischemia sometimes develops proximal to a carcinoma of the colon (Fig. 14). It is therefore important to rule out a neoplasm by appropriate clinical and radiologic studies in all patients with vascular disease of the colon. The mechanism of the development of ischemia in association with colonic carcinoma is unclear, but experimental studies suggest that large bowel obstruction and distention may be responsible for interference with the intramural blood supply proximal to the neoplastic lesion (7).

Bleeding into the wall of the colon caused by coagulation disorders and by trauma is uncommon. When it does occur, mural bleeding causes scalloped defects along the contour of the bowel, with narrowing of the lumen (Fig. 15). Usually the blood is resorbed, and the defects disappear on subsequent examinations.

Summary

In summary, the characteristic radiographic features of ischemia of the colon are thumbprinting, thickening of the folds, pseudosacculations, tubular narrowing, and stricture. The differential

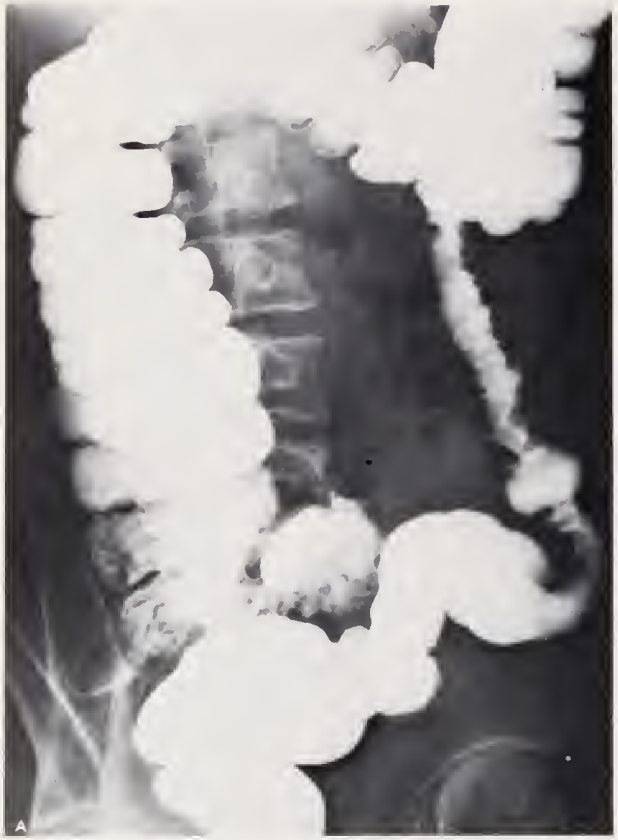


FIG. 12A. Reversibility in ischemia of the colon. A 68-year-old male with sudden onset of abdominal pain and rectal bleeding. Barium enema reveals typical changes of ischemia in the descending colon.

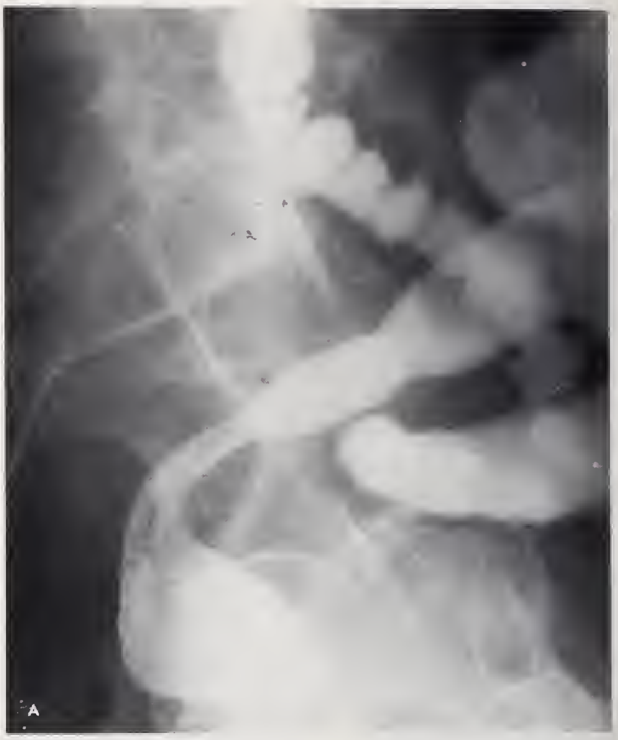


FIG. 13A. Ischemia of the rectum is not common. This cardiologist experienced an episode of abdominal pain and bleeding while attending a medical meeting. Barium enema reveals narrowing of the rectum and sigmoid.

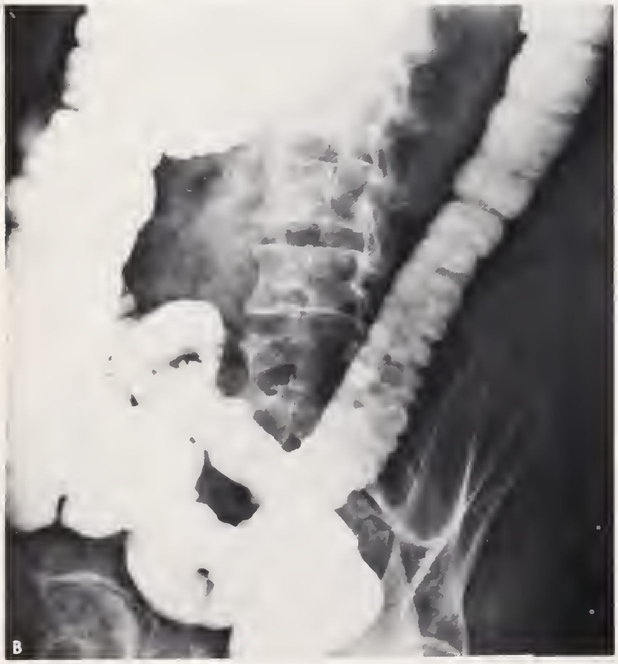


FIG. 12B. Same case as 12A, six weeks later. The bowel has returned to normal.

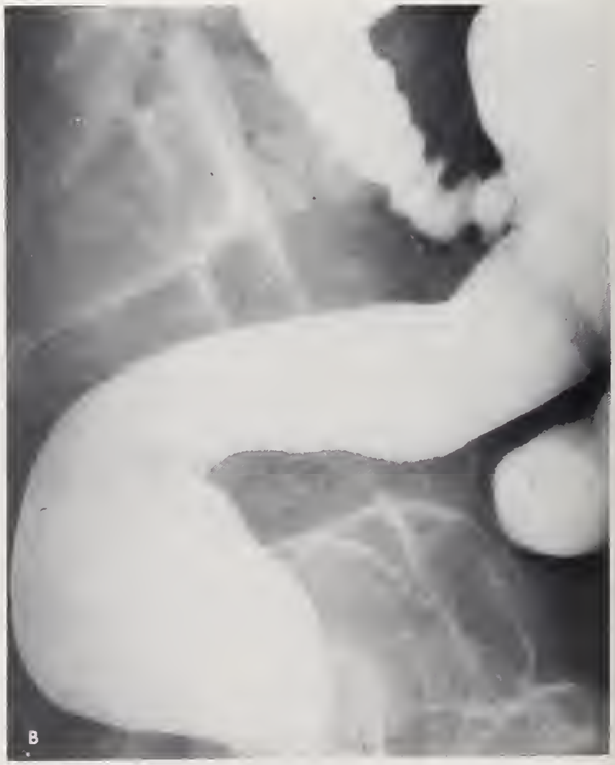


FIG. 13B. Same patient as 13A. One month later complete reversal of the findings is observed.

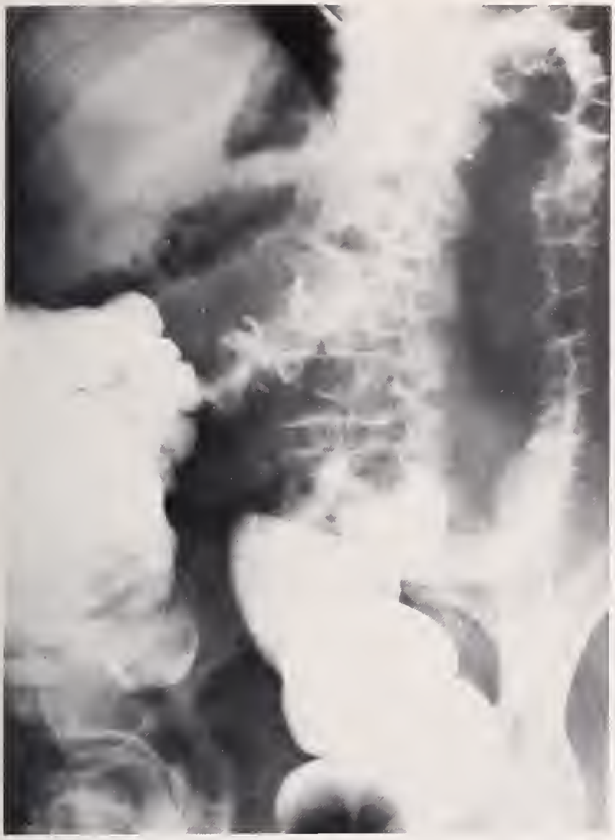


FIG. 14A. Ischemia of the colon proximal to a carcinoma.

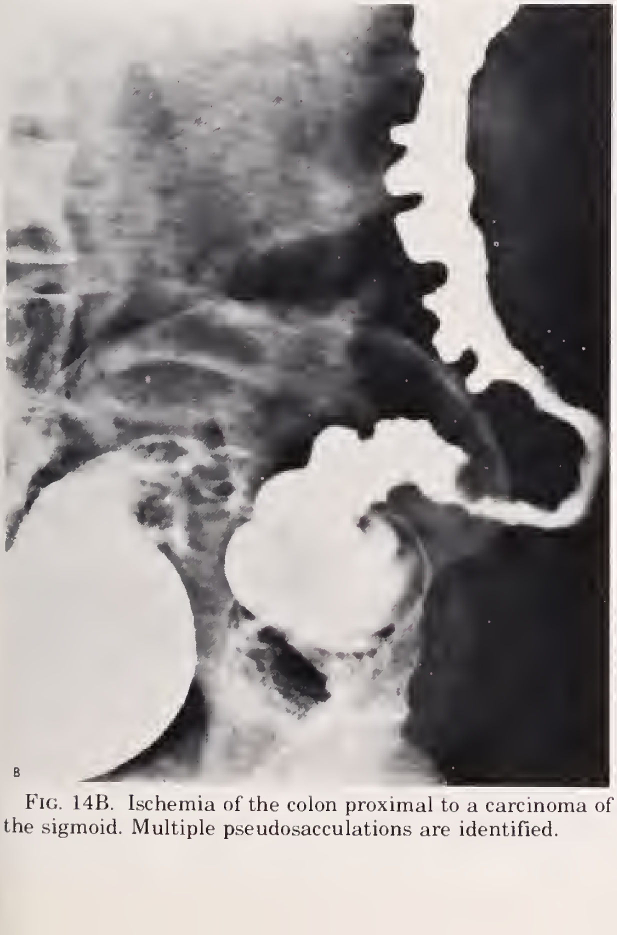


FIG. 14B. Ischemia of the colon proximal to a carcinoma of the sigmoid. Multiple pseudosacculations are identified.

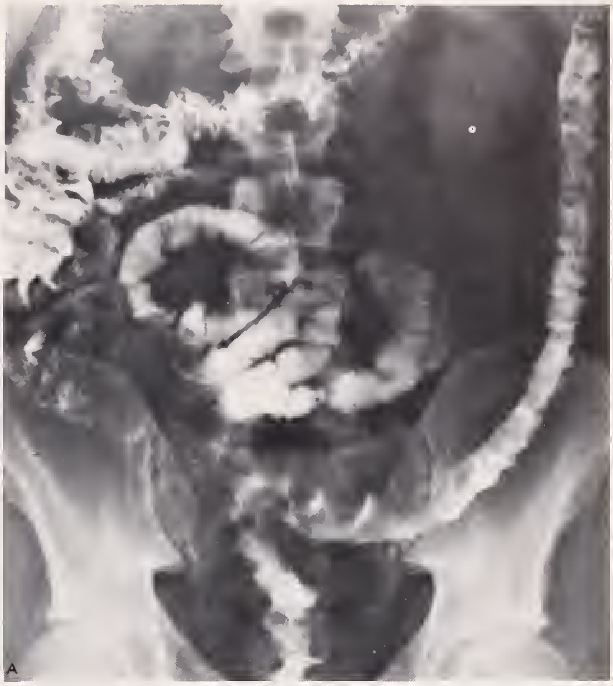


FIG. 15A. Intramural bleeding in the colon simulating ulcerative colitis. The rectum, sigmoid, and left side of the colon demonstrate narrowing, limited distensibility and early thumbprinting. Increased secretions are also seen. The patient had heart disease and was receiving anticoagulants. The findings returned to normal after anticoagulant therapy was discontinued. With modern methods for control of anticoagulant therapy, these lesions are now rare.

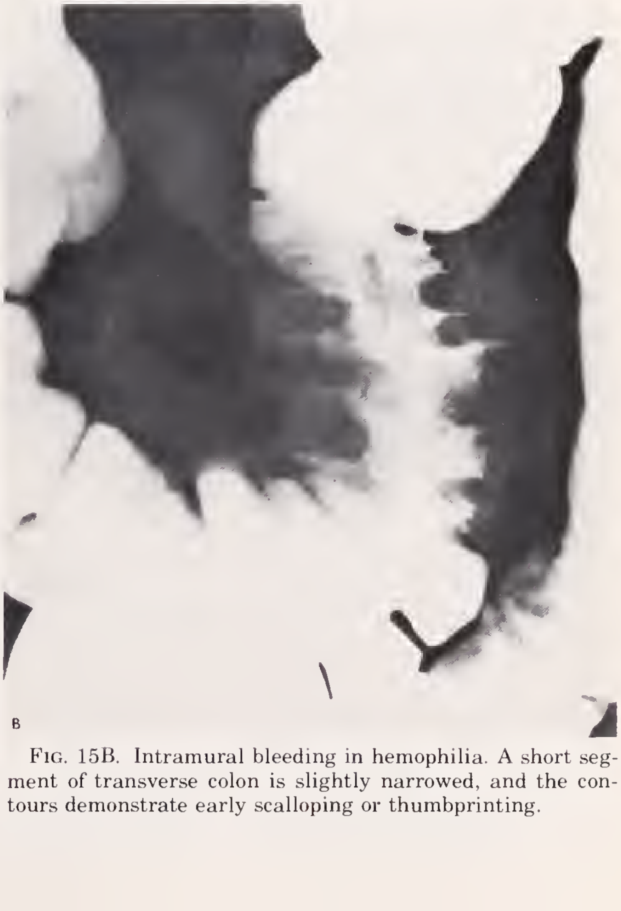


FIG. 15B. Intramural bleeding in hemophilia. A short segment of transverse colon is slightly narrowed, and the contours demonstrate early scalloping or thumbprinting.

diagnosis includes carcinoma and granulomatous inflammatory disease. The stricture of infarction is smooth and tapering, with a concentric lumen and without overhanging margins or contour defects. Skip lesions are unusual, but sacculations are common. In contrast to these findings, the frequent features or granulomatous disease are cobblestoning, skip lesions, and small punched-out ulcers. Carcinoma demonstrates overhanging margins, eccentric lumen, and, in the early stages, a contour defect.

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Complications of Gastrointestinal Endoscopy

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The technical refinements and widespread application of modern flexible fiberoptic endoscopes have significantly improved the diagnosis of gastrointestinal disorders. Nevertheless, some of the resultant iatrogenic trauma may not be readily apparent to the endoscopist during the procedure or may have delayed clinical manifestation. Radiologic evaluation documents the occurrence and the extent of many of the major gastrointestinal complications of fiberoptic endoscopy.

Upper Gastrointestinal Endoscopy

A survey of the members of the American Society for Gastrointestinal Endoscopy has shown an overall complication rate of 1.32/1000 peroral endoscopic examinations (1). The complication rates for esophageal dilatation ranged from 4.25 to 18.4 per thousand cases. Major complications included perforation, hemorrhage from biopsy, aspiration, myocardial infarction, cardiac arrest and arrhythmia, and respiratory arrest.

The more frequent use of upper gastrointestinal fiberendoscopy, replacing the previously standard semirigid instruments, has led to a definite increase in both the actual number of perforations and mortality (2). Radiologic examination is the most valuable diagnostic test in suspected esophageal or gastric perforation (2–5).

Esophageal Perforation

The most common cause of esophageal perforation continues to be instrumentation during esophagoscopy, gastroscopy, or esophageal dilatation (3, 5). Fiberesophagoscopy alone carries a perforation rate of nearly 0.1%, representing no significant improvement in safety over older semirigid esophagoscopes.

Fiberscope induced perforation of an anatomically normal esophagus may occur (6), but the risk is even greater if the esophageal wall is involved by an inflammatory or neoplastic process, particularly when endoscopy is combined with biopsy or dilatation of a stricture (5). Davis (7) emphasizes that "in final perspective, however, every such perforation must be considered an error in technique no matter how unusual the anatomy, how poorly the patient cooperates, or how skillful the endoscopist." Early diagnosis is essential since successful management requires prompt and vigorous treatment. The mortality rate is 9%–31% (3, 5, 8). The prognosis is even less favorable if mediastinitis is complicated by involvement of the pleural spaces. Treatment generally requires antibiotics and surgical drainage and, if possible, primary closure (9, 10).

Cervical esophageal perforation may be caused by the tip of the instrument becoming engaged in the pyriform sinus laterally or causing the posterior pharyngeal wall to bulge above the cricopharyngeal muscle (Fig. 1). Contributory factors include faulty positioning of the head, lack of control of the tongue, or gagging. When perforations have occurred in this region, the operator has usually been astonished at the lack of any sensation of rupture. Lateral radiographs of the neck almost invariably demonstrate evidence of air in the prevertebral space followed, perhaps, by signs of retropharyngeal abscess formation. Esophagography with water-soluble contrast medium may reveal the site of perforation in only 50% of cases (5). It is more valuable in perforations of the thoracic esophagus, showing extravasation at the site in 75%–86% (3–5). Chest radiographs are also important since they facilitate evaluation of the extent of spread and possible development of further complications. Plain films may show mediastinal or subcutaneous air, pneumothorax, widening of the mediastinum, and pleural fluid.

Perforation of the cervical esophagus sometimes extends down the mediastinum for a considerable length (Figs. 1, 2) (2, 11). Treatment usually requires cervical mediastinotomy with drainage of the prevertebral space (5) but occa-

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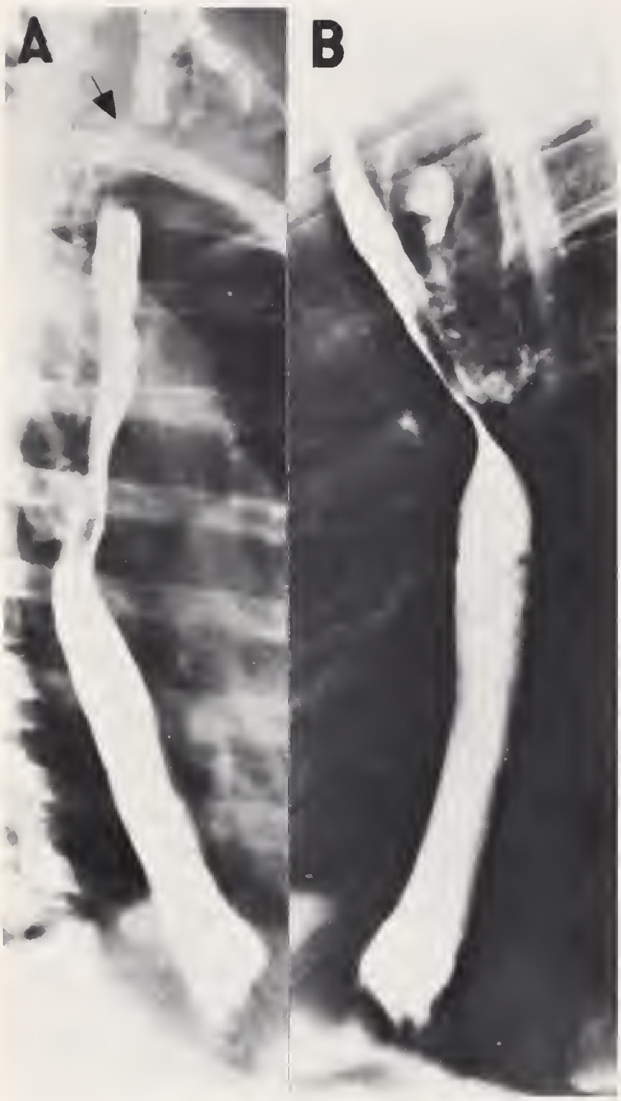

FIG. 1. (A and B). A 41-year-old woman underwent unremarkable fibergastroscopy. Following the development of cervical subcutaneous emphysema shortly after the procedure, a chest radiograph showed pneumomediastinum. Examination with water-soluble contrast material documented extravasation through a 6 mm perforation of the cervical esophagus at the level of C7. Under therapy with antiobitics and parenteral feeding, the patient appeared to improve; however, ten days later, this barium study not only again showed the posterior perforation of the lower cervical esophagus (arrow) but also revealed its extension into a loculated abscess cavity extending below the level of the aortic arch in the retroesophageal mediastinal tissues. This was subsequently drained, and follow-up studies showed no further communication. From Meyers MA, Ghahremani GG (2).

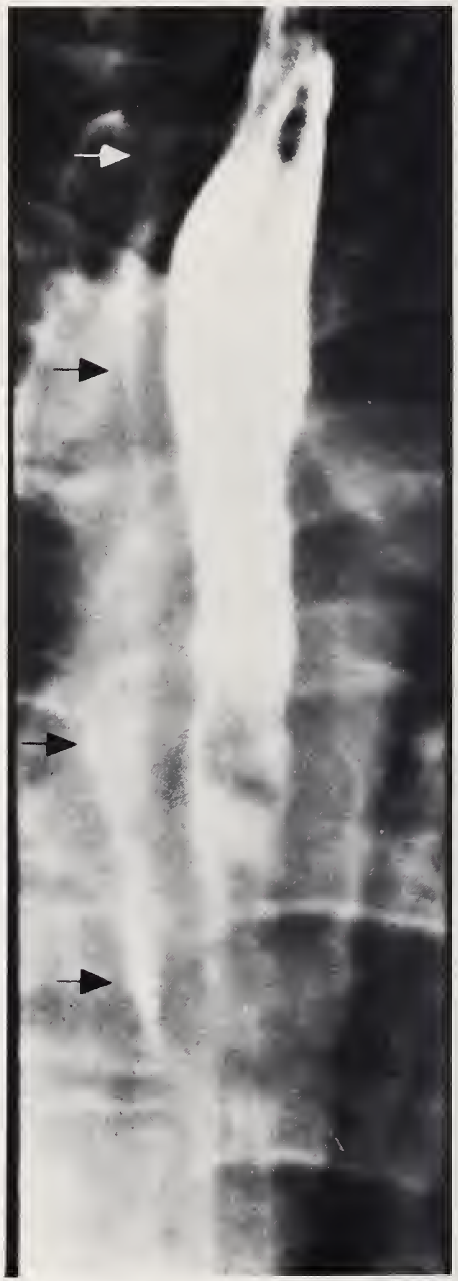

FIG. 2. This patient presented with cervical subcutaneous emphysema and dysphagia following fiberesophagoscopy. A deep mediastinal sinus tract (arrows) extends to the level of T8 due to perforation of the pharynx. From Meyers MA, Ghahremani GG (2).

sionally prompt conservative management may be successful (2).

Another anatomic point of narrowing of the esophagus that may present some difficulty to instrumental passage is at the level of a tortuous aortic arch and the left main bronchus (Fig. 3) (2). Acquired friable strictures may develop at these same points of narrowing, further increasing the possibility of perforation from endoscopy, biopsy, or dilatation (Fig. 4).

Perforations commonly occur in the lower third of the esophagus and were found primarily at this site in several series (Fig. 5) (3, 4, 10). This may be due to thinning and segmental defects in the circular layer of the muscle at the lower end of the esophagus, the segment most frequently involved

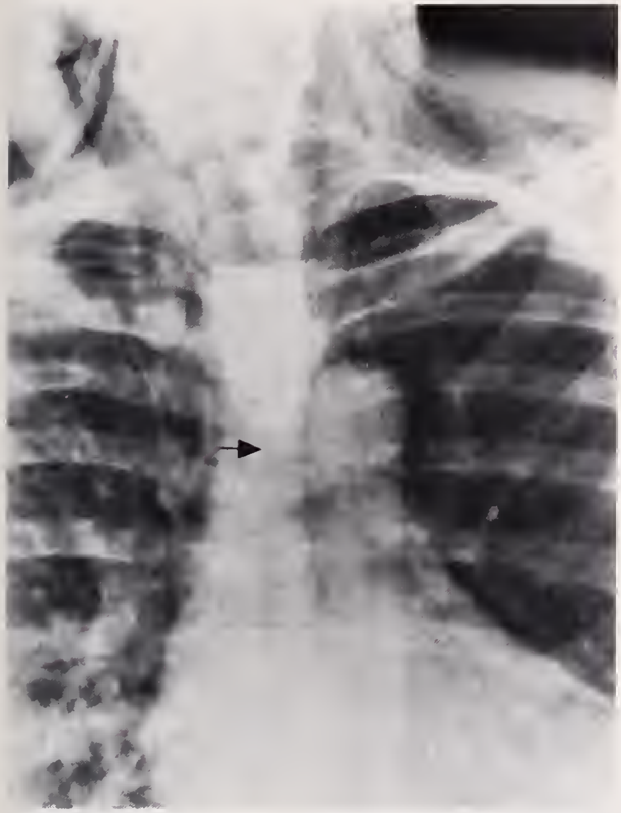

FIG. 3. Fibergastroscopy was discontinued because of excessive resistance in the lower esophagus in this patient and the rapid development of massive subcutaneous emphysema. On this posteroanterior chest film with water-soluble contrast material in the esophagus, note the partial esophageal obstruction at the level of anatomical narrowing at the aortic arch and left main bronchus (arrow). Considerable pneumomediastinum and subcutaneous emphysema are evident. Immediate exploratory mediastinotomy showed perforation of the cervical esophagus with a false passage into the thoracic mediastinum, accompanied by a localized perforation and hematoma in the mid thoracic esophagus. The patient responded well to drainage and chest intubation. From Meyers MA, Ghahremani GG (2).

by inflammation or neoplasm. Endoscopic perforation through an inflammatory stricture or carcinoma (Fig. 6) can occur with surprising ease. Cohen and Katz (12) reported 29 patients with esophageal carcinoma who had radiologic evaluation with contrast material following esophagoscopy. A total of 45% had esophageal perforation. In three patients, the trauma could be directly attributed to esophagoscopy, since chest films and esophagograms were obtained both before and after the procedure. Of the 13 patients with esophageal perforation, only one presented with symptoms of mediastinitis or pneumonitis. Conservative medical treatment may suffice in some patients with small perforations with minimal signs of leakage (3).

Endoscopic biopsy of a friable lesion may also result in perforation. Although biopsy is usually superficial and produces no complication, mural transgression can result if an area of ulceration, a weakened wall, or relative ischemia is entered (Fig. 7) (2, 5, 8).

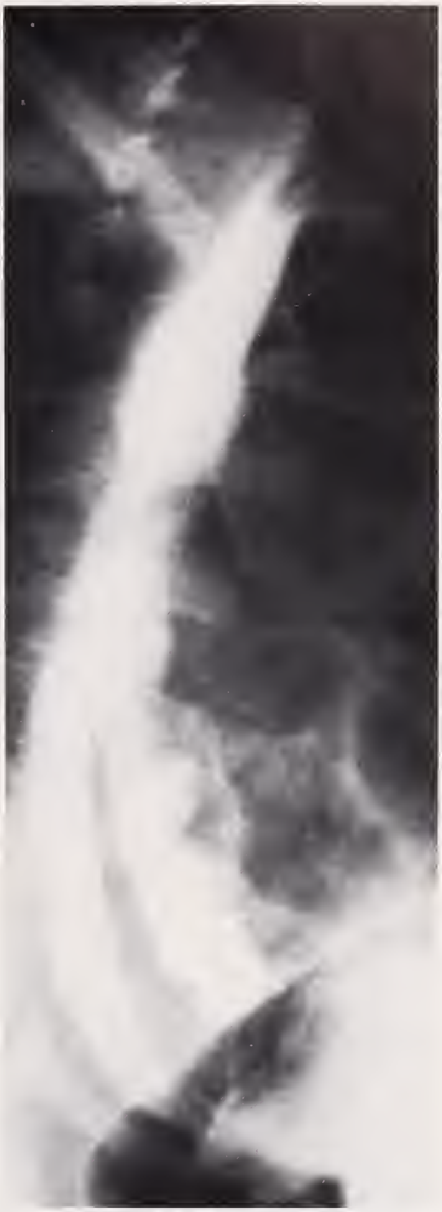

FIG. 4. Corrosive esophagitis with a large mediastinal sinus tract following fiberesophagoscopy. Perforation occurred at the site of a lye stricture which developed at the anatomical narrowing at the level of the left main brochus. The tract extends to the level of the diaphragm, presenting the appearance of a double esophagus. From Meyers MA, Ghahremani GG (2).

Impaction of the Fiberscope

Despite its flexibility and sometimes because of it, the instrument may curve back upon itself and become impacted within the esophagus (2,

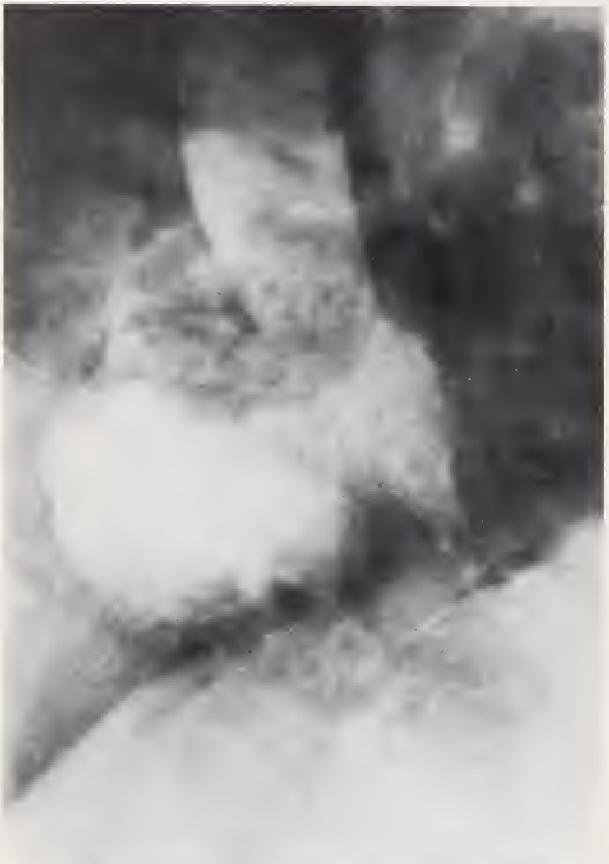

FIG. 5. Loculated mediastinal collection following fiberscopic perforation of the distal esophagus after removal of impacted piece of meat. From Meyers MA, Ghahremani GG (11).

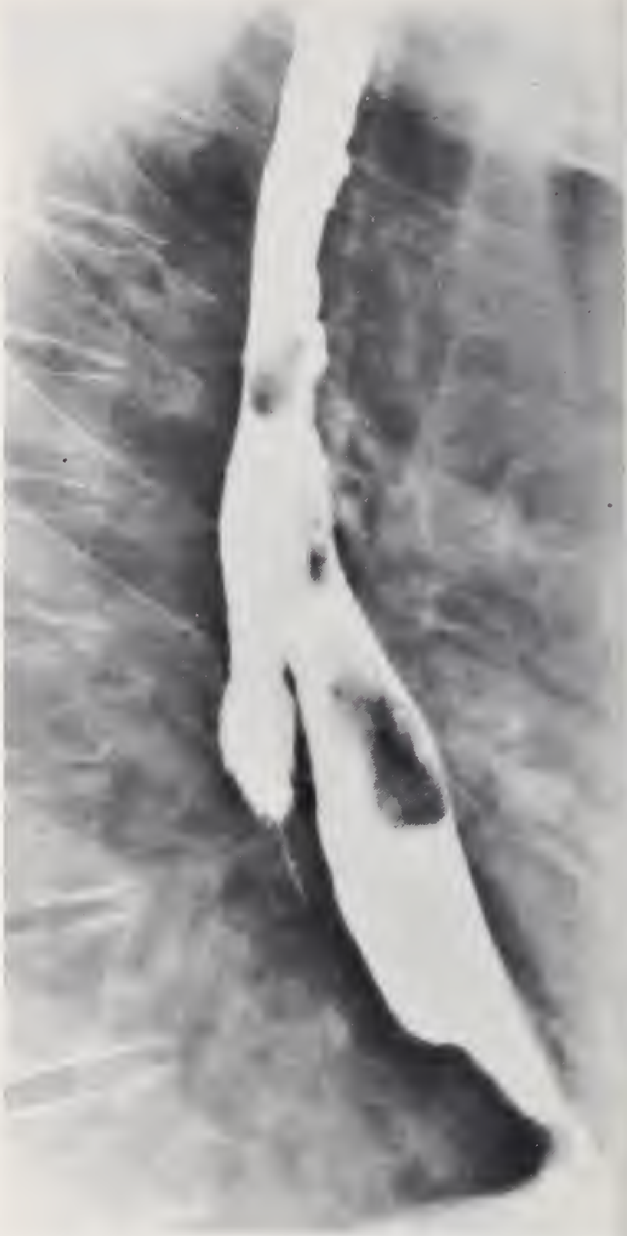

FIG. 6. Carcinoma of the esophagus with a large mediastinal sinus tract secondary to fiberesophagoscopy. From Meyers MA, Ghahremani GG (11).

13–15). The reason for the difficulty in further passage and the occasionally unexpected field of visualization is readily confirmed radiologically. The impacted endoscope has been withdrawn in its looped position (13), straightened with a Jackson esophagoscope (14), and advanced into the stomach, straightened, and then withdrawn (15).

Within the stomach, inversion gastroscopy or retroflexion of the distal tip of the instrument to visualize the fundus has also resulted in impaction (16, 17). This complication occurs within a small gastric pouch, in the fundus of a cascade stomach, or within a hiatus hernia. Considerable manipulation under fluoroscopic control may be helpful in reducing the impaction, but an emergency laparotomy may be unavoidable (18).

Gastric Perforation

Within the stomach, perforation usually occurs posteriorly into the lesser sac at or just beyond the esophagogastric junction (19). This can be explained on an anatomic basis, since just beyond the cardia, the posterior wall is angulated anteriorly by the bulk of the retroperitoneal organs. Trauma at this site, ranging from intramural hematoma (Fig. 8) to true rupture, may also be induced by the fibergastroscope. The most frequent and characteristic endoscopic sign of gastric perforation is the inability to inflate the lesser sac, since air escapes through the foramen of Winslow to produce a pneumoperitoneum.

Water-soluble contrast studies may not demon-

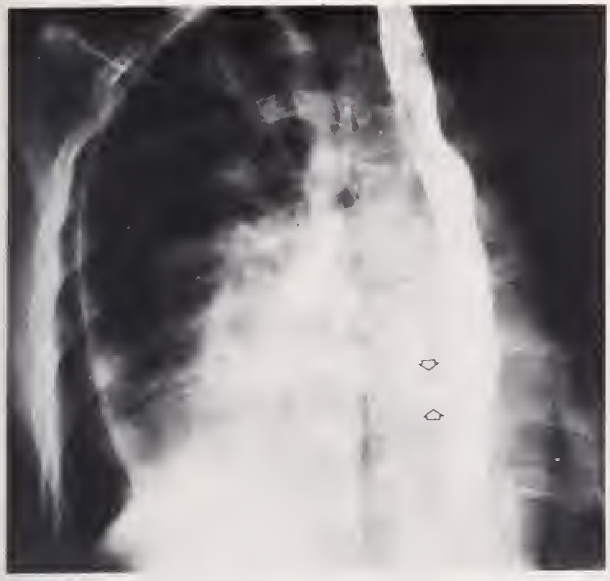

FIG. 7. Following fiberesophagoscopy and multiple biopsies of an ulcerated esophageal carcinoma, the site of an esophagopleural fistula (arrows) is documented with water-soluble contrast material. The patient died following a complicated postoperative course. From Meyers MA, Ghahremani GG (2).

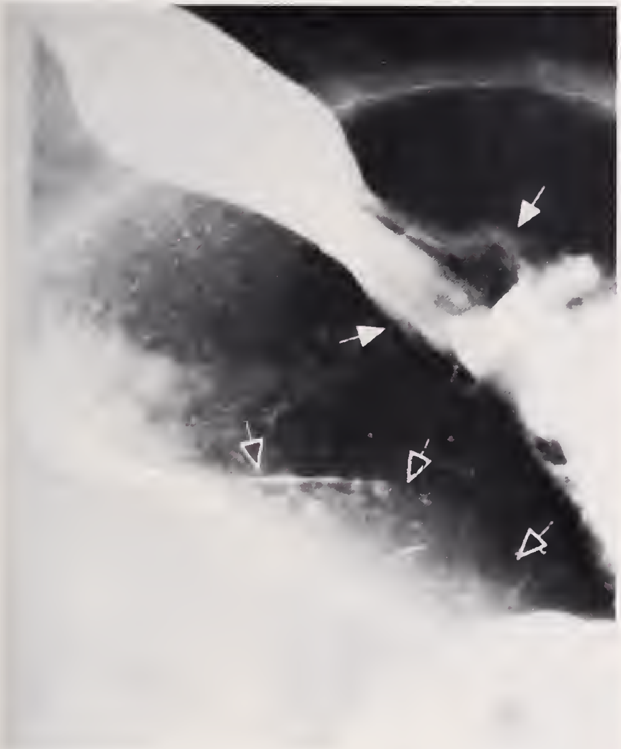

FIG. 8. Hematomas of the cardia (closed arrows) and posteromedial wall of the gastric fundus (open arrows) induced by fibergastroscopic trauma. From Meyers MA, Ghahremani GG (2). (Courtesy of Jack Farman, M.D. SUNY Downstate Medical Center, Brooklyn, N.Y.)

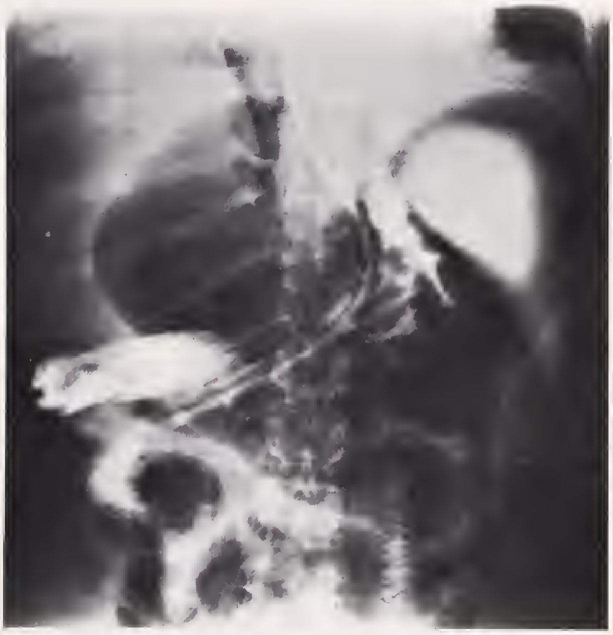

FIG. 9. Fibergastroscopy-induced perforation of the stomach into the lesser sac. Water-soluble contrast material introduced through the nasogastric tube demonstrates the position of the stomach. Extravasation posteriorly into the lesser sac, grossly outlined by free air within it, has occurred via a perforation near the cardia and gravitated to the area of the splenic bed at the site of a previous splenectomy. From Meyers MA, Ghahremani GG (2).

strate extravasation, and a perforation has not been found in almost half of the patients undergoing laparotomy for this complication (19). However, Calem (19) has shown that the usual site of a gastric perforation is easily overlooked during routine exploratory laparotomy. The posterior wall of the stomach in the area of the fundus and gastroesophageal junction is comparatively inaccessible unless the stomach is well mobilized. He has demonstrated that mechanical perforation of the stomach does indeed occur, often with a rent as large as 1.5 cm, but tends to be self-sealing. Thus, it has become accepted that conservative therapy based on continuous gastric aspiration and prophylactic antibiotic administration is generally preferable to emergency laparotomy, since the stomach is empty at the time of perforation and the escaping gastric juice is nearly sterile (19). Usually the clinical course is surprisingly benign, without evidence of peritoneal irritation; at other times, however, extravasation into the lesser sac from a large posterior gastric perforation can be demonstrated radiologically (Fig. 9), and these patients are best treated surgically.

Endoscopic perforation through the anterior wall of the stomach is usually the result of instrumental passage through a lesion or transmural penetration following biopsy (Figs. 10–11) (2) and typically presents more serious and immediate consequences; the rent is not self-sealing and leads to peritonitis or a localized abscess. In-

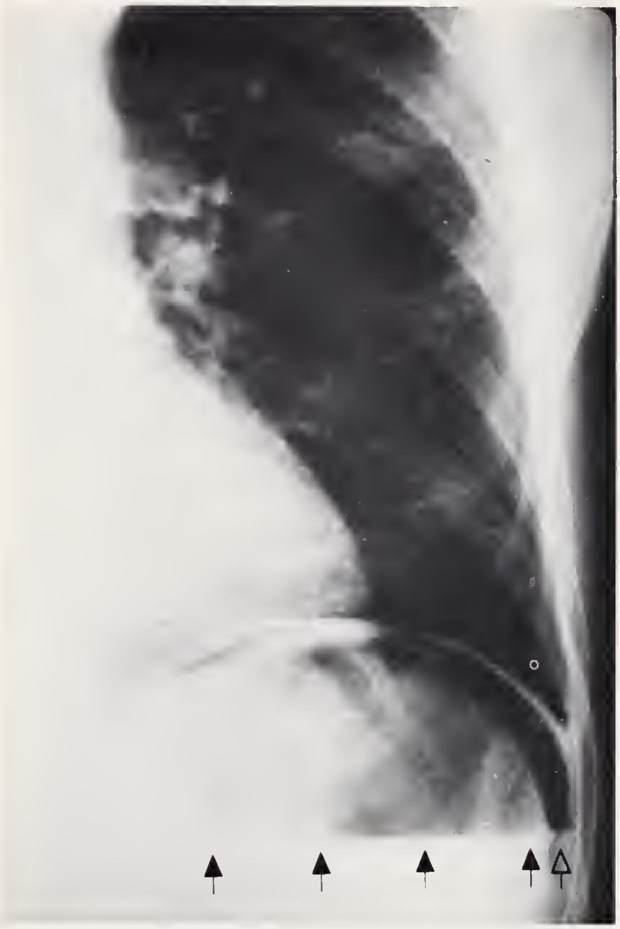

FIG. 10. At fibergastroscopy and biopsy of a polypoid adenocarcinoma of the gastric fundus, a perforation occurred anteriorly in the periphery of the tumor. The erect film shows a subphrenic air-fluid collection. Note that the intraperitoneal fluid level (open arrow) is on the same plane as that within the stomach (closed arrows), indicating communication between the gastric lumen and the incipient subphrenic abscess. The soft-tissue tumor mass is evident within the fundus. From Meyers MA, Ghahremani GG (2).

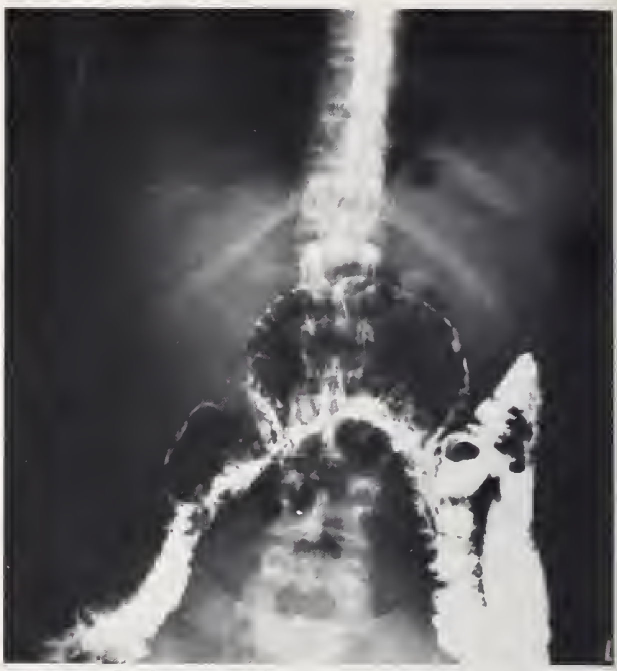

FIG. 11. Perforation of the greater curvature of the stomach following endoscopic biopsy of carcinoma. Erect film of the abdomen. Residual contrast material in transverse colon demonstrates effects of paresis secondary to extension of perforation along the gastrocolic ligament. Free intraperitoneal air is also evident. From Meyers MA, Ghahremani GG (11).

tramural hematoma may be seen as a less serious consequence (Fig. 12) (11).

Pseudo-acute Abdomen following Gastroscopy

New instruments with a powered air supply are capable of introducing large volumes of air during endoscopy, leading to considerable acute gaseous distention of the small bowel. The dramatic clinical picture of severe abdominal pain, distention, and diffuse tenderness may be mistaken for perforation (20, 21). Prompt radiologic evaluation should indicate the true condition.

Submandibular and Parotid Swelling

Submandibular swelling is an unusual complication but deserves brief attention because of its

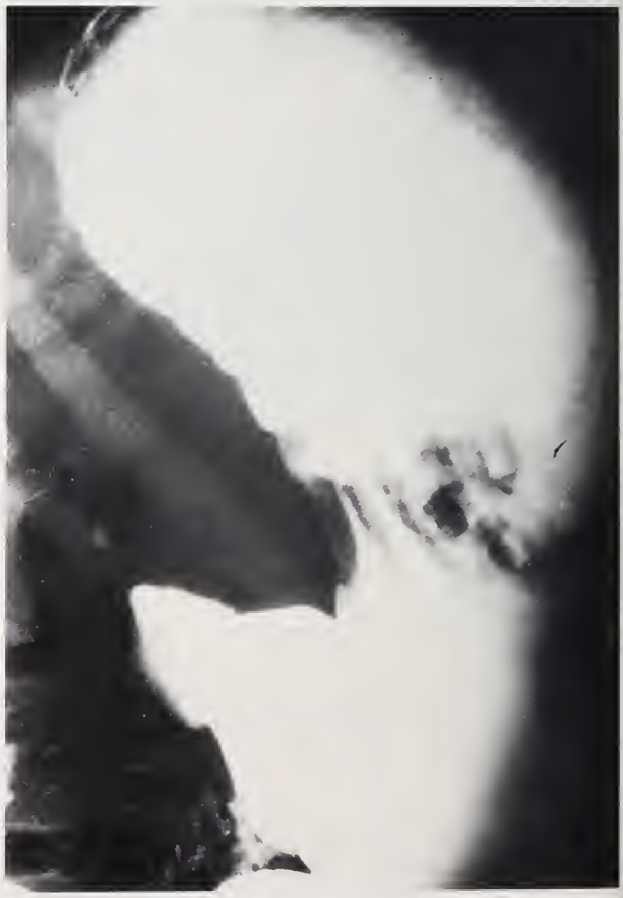

FIG. 12. Intramural gastric hematoma secondary to fiberoptic endoscopy. From Meyers MA, Ghahremani GG (11).

rather confusing clinical presentation. In patients with persistent blind remnants of the fourth branchial cleft, insufflation of air during the procedure can result in bilateral swelling below the parotid glands. The air can easily be evacuated by manual compression of these branchial pouches (22). The submandibular glands may also swell because of ductal obstruction caused by displacement of these organs during the endoscopic procedure (23). Spontaneous regression of symptoms usually occurs within a few hours.

Aspiration Pneumonia and Other Complications

Pharyngeal motor dysfunction of mild degree and short duration is not uncommon after gastrointestinal endoscopy and is usually caused by topical anesthesia and the mild trauma induced. Delayed clearing of contrast material from the hypopharynx of several patients up to two days after uncomplicated gastrointestinal fiberendoscopy has been noted (2) and this may also explain the occasional development of aspiration pneumonia in such cases. Patients with obstructive lesions and functional disorders of the esophagus are prone to aspiration even without the contributory effects of a traumatic endoscopy.

Hematemesis may be associated with perforation. Clinically significant hemorrhage very seldom occurs following fiberendoscopic biopsy of gastroesophageal lesions, since small samples are obtained under good visibility. Nevertheless, a bleeding diathesis, acute phlegmonous and corrosive esophagitis, and gastroesophageal varices are still contraindications to biopsy.

Colonoscopy

Fiberoptic colonoscopy is being used increasingly for endoscopic visualization of the large intestine, particularly in the removal of colonic polyps using an electrosurgical snare advanced through the biopsy channel of the colonoscope. Despite the relative flexibility of the instrument and the removal of polyps by cauterization under direct visualization, several complications have been encountered. Radiologic examination plays a decisive role in the initial identification and documentation of many complications (2, 11, 24). The one that occurs most frequently and requires prompt diagnostic evaluation is perforation of the colon.

Technical Considerations

Fiberoptic colonoscopes of varying lengths permit endoscopic evaluation of the colon from the rectum to the cecum. Passage through the rectum is performed under direct vision, but negotiation through the sigmoid is usually accomplished without complete visualization of the lumen (25). Visualization of the entire wall of the colon is carried out primarily during withdrawal. Often, some difficulty in passage of the instrument is encountered at the points of curvature of the rectosigmoid and the junction of the sigmoid and descending colon, and too much "persuasive pressure" (26) in advancing the scope may result in mural perforation. Marked redundancy of the colon and narrowing or angulation due to diverticulosis, previous inflammatory processes, or extrinsic compression of the lumen by pelvic masses may make negotiation difficult.

Gaseous distention of the colon is used to facilitate passage of the instrument. Initially, because of the presence of the combustible gases hydrogen and methane in the colon, carbon dioxide was introduced to avoid colonic explosion during cautery. Room air is now generally used because the adequately cleansed colon is free of putrefactive gases and the gas content of the bowel is exchanged several times during introduction of the colonoscope (28, 29).

While advancement of the colonoscope may be monitored fluoroscopically, most endoscopists employ fluoroscopy or abdominal radiography only when difficulty is met (25, 28).

Colonoscopic Perforations

An American Society for Gastrointestinal Endoscopy survey has shown that the most common complication of diagnostic colonoscopy is perforation (0.22%). Furthermore, colonoscopic polypectomies resulted in perforation in 0.29% of cases, although its most common complication was hemorrhage (1.9%) (27). Others have reported a perforation rate as high as 1.9% with initial experience in colonoscopy (30).

The most common sites of mural perforation during diagnostic colonoscopy include the rectosigmoid and the junction of the sigmoid and descending colon (24, 27). Many occur during mechanical manipulations, including the techniques of slide-by, alpha maneuver, and straightening of the sigmoid loop. Friability of the wall from inflammatory colitis is a recognized hazard.

The colonoscope may also be advanced into a prominent diverticulum, causing its orifice to be mistaken for the proximal continuation of the colonic lumen. Insufflation of the colon by gas has also been incriminated in diverticular perforation.

Colonoscopic fulguration of polyps has wide application but may also result in serious complications. A loop of wire is advanced through the biopsy channel of the colonoscope and electric current is applied while the snare is closed around the pedicle or base of the polyp. Large, sessile lesions may have to be removed in piecemeal fashion (28). Overzealous application of heat, inadvertent inclusion of a portion of the colonic wall in the cautery snare, or unclear visualization of the snare in the center of the bowel lumen while touching a point on the opposite wall may produce coagulation necrosis and resultant perforation (24).

Free (intraperitoneal) perforation is about four times more frequent than closed (extraperitoneal) perforation, both in diagnostic colonoscopy and following polypectomy.

Clinically, perforation may be recognized immediately or there may be considerable delay. Intraperitoneal rupture is usually immediately apparent but may be initially overlooked, particularly in the aged or infirm patient (24). Prompt surgical closure is generally indicated. Extraperitoneal perforation may be masked for several hours or days (24) and is often not evident by the usual clinical modalities of auscultation, palpitation and percussion. Indeed, it may not be until the extraperitoneal gas extends to the abdominal wall, mediastinum, or cervical tissues that it first becomes clinically apparent. However, extraperitoneal rupture generally follows a more benign course and can be treated conservatively. We have recommended routine abdominal radiography following diagnostic and therapeutic colonoscopy (24). Because the colon is distended for easier endoscopic passage and visualization, considerable extraluminal gas is usually apparent if rupture has occurred.

Free intraperitoneal air is indicated on a supine film by increased radiolucency, visualization of the falciform ligament and perhaps the umbilical folds, and demonstration of both sides of the bowel wall (Figs. 13, 14). Erect or decubitus films readily demonstrate free intraperitoneal air.

Extraperitoneal perforation most commonly involves the rectum or the posterior wall of the descending colon. Perforation of the sigmoid or transverse colon into the mesentery and of most diverticula also extends posteriorly as extraperitoneal gas (31). Radiographic findings not only may reveal that a perforation has occurred but may also indicate the site of the rupture (31).

Rectal perforation is indicated by gas ascending the posterior pararenal spaces bilaterally, with lucent areas paralleling the lateral borders of the

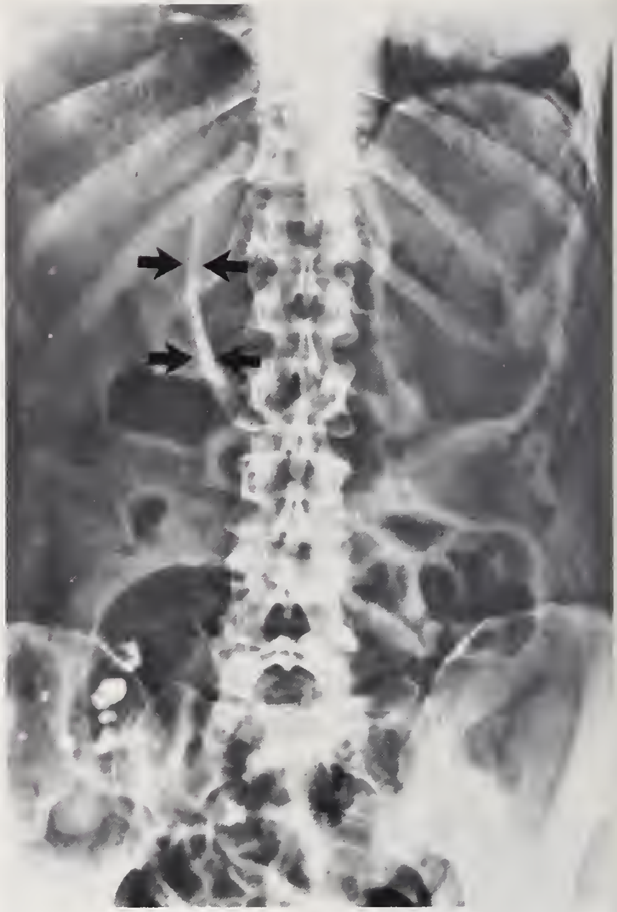

FIG. 13. Sigmoid perforation secondary to coagulation necrosis of the colonic wall at colonoscopic polypectomy. Gross free intraperitoneal air causes lucent distension of the abdomen and allows visualization of the falciform ligament (arrows). From Meyers MA, Ghahremani GG (24).

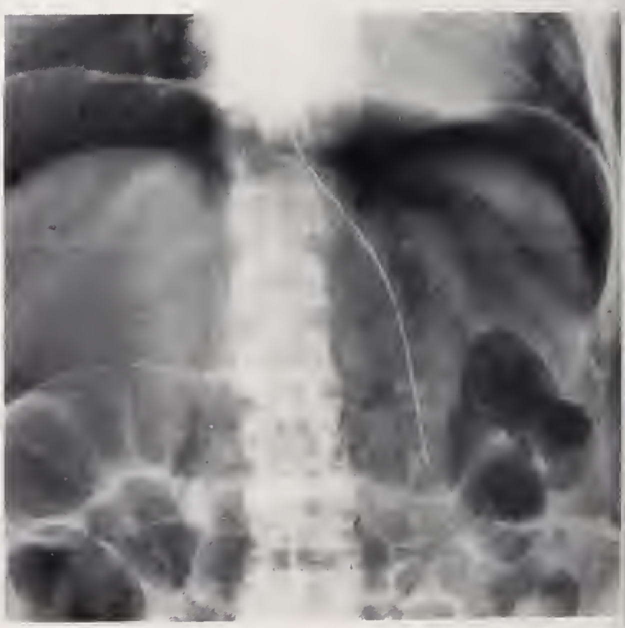

FIG. 14. Sigmoid perforation occurring during the alpha maneuver. Erect abdominal film demonstrates free subdiaphragmatic gas bilaterally, with visualization of the bowel wall. From Meyers MA, Ghahremani GG (24).

psoas muscles; superiorly, it sometimes extends as high as the upper renal pole and adrenal gland, the medial border of the spleen and liver, the medial crus of the diaphragm, and the immediate subphrenic tissues (Fig. 15). Extension into the flank fat stripes, anterior abdominal walls, scrotum, and mediastinum may occur.

Extraperitoneal (posterior) perforation of the sigmoid, descending, or ascending colon results in a unilateral collection of gas within the anterior pararenal space, shown by a collection of mottled lucent areas with a generally vertical axis. These characteristically extend medially over the psoas muscle to approach the spine but do not usually infiltrate the flank stripe (Fig. 16). Perforation of the sigmoid colon at a site between the leaves of the mesocolon may give rise to extraperitoneal gas within the anterior pararenal spaces bilaterally. Both intra- and extraperitoneal gas may be seen, depending upon the site of the colonic perforation. These plain film observations become particularly crucial in that emergency enemas with water-soluble contrast material may not directly demonstrate the site of colonic perforation (32). Radiologic localization of the precise site is important in locating a clinically uncertain site of perforation, indicating the proper treatment, and anticipating possible complications.

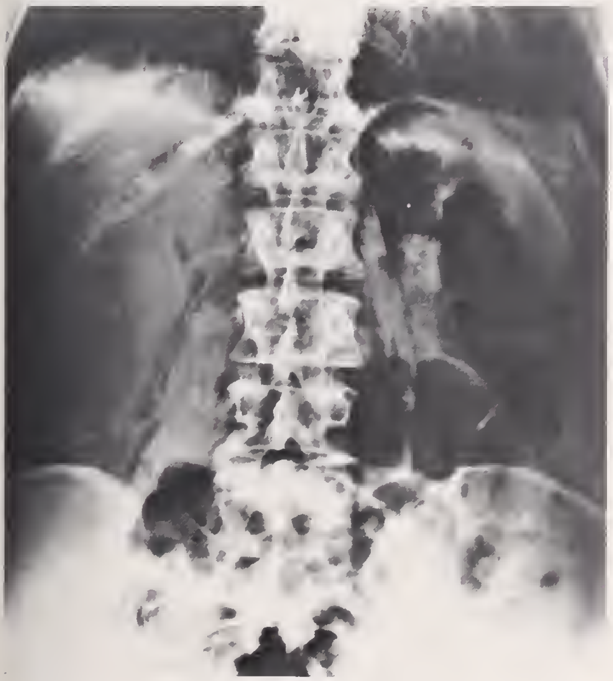

FIG. 15. Rectal perforation secondary to colonoscopy. Erect film demonstrates extraperitoneal gas paralleling the lateral borders of the psoas muscles. Cephalad extension on the left outlines the upper pole of the kidney, the adrenal gland, the medial border of the spleen, the medial crus of the diaphragm, and the immediate subphrenic tissues. These findings localize the gas to the posterior pararenal compartments. From Meyers MA (31).

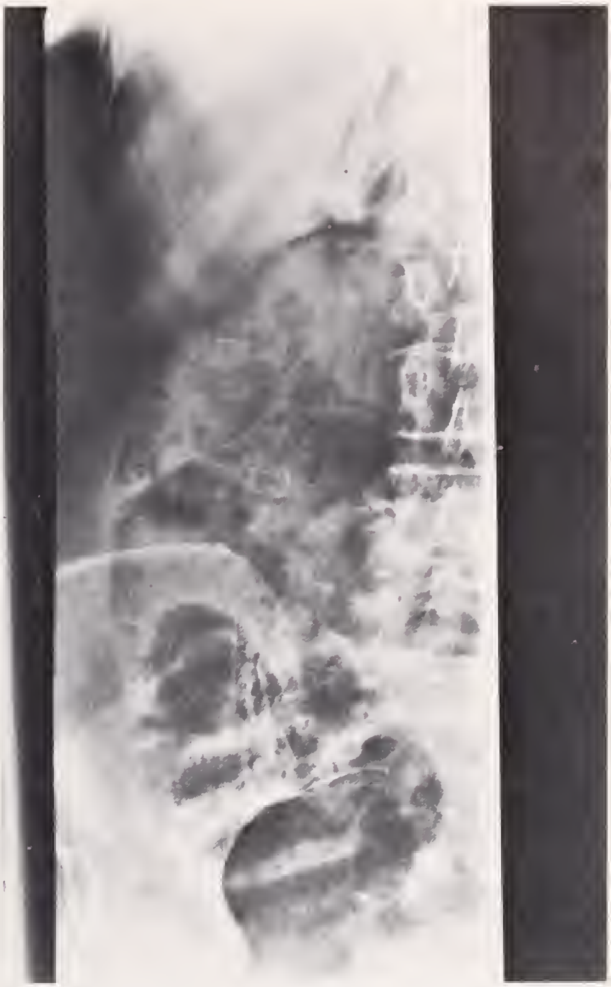

FIG. 16. Perforation of the hepatic flexure following colonoscopic polypectomy. Mottled lucent areas on the right represent collections of gas extending medially over the psoas muscle and approaching the spine. The flank stripe is intact. These changes localize the extraperitoneal gas to the anterior pararenal space. From Meyers MA, Ghahremani GG (24).

Other Complications

A spectrum of other complications has also been experienced. Insufflation of gas to facilitate passage of the colonoscope occasionally may cause massive and prolonged dilatation of the small intestine in patients with a patulous ileocecal valve (11). Mural perforations by the colonoscope at the site of a stricture may result in a localized abscess. A hematoma may develop in the sigmoid mesentery as the result of difficulty in passing the instrument or attempts to alter or bypass the redundant curvature of the sigmoid loop (11). Serosal lacerations or seromuscular tears, often clinically occult, have also been encountered due to mechanical pressures of the instrument (33–35). Problems may also occur during withdrawal of the instrument. Reported complications include incarceration of the colonoscope in an unsuspected inguinal hernia and avulsion and rupture of the spleen, presumably secondary to instrumental intussusception of the colon (24).

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Metastasis Versus Pancreatitis Affecting the Transverse Colon

JOAN ELIASOPH, M.D.

Abstract

Two cases illustrate the similarity of the roentgen findings in secondary involvement of the transverse colon by carcinoma of the stomach and pancreatitis. Because the presenting complaint is most often abdominal pain, barium enema may be the first diagnostic examination performed. Careful analysis of the secondary involvement of the colon may lead to the original source of disease. The importance of establishing the correct diagnosis in a sometimes confusing situation cannot be too greatly stressed.

The transverse colon can be a sensitive indicator of disease elsewhere in the abdomen. Because of its long course, both intra and extraperitoneal, with its many peritoneal attachments and close proximity to the other organs, signs and symptoms of disease elsewhere may point strongly to disease of the large intestine. Accordingly, a barium enema is often considered the most logical first procedure. The altered appearance of the transverse colon, while not necessarily intrinsically involved, may suggest the problem area and, in fact, focus the direction of further study. Segmental involvement of the transverse colon by extrinsic processes has been documented frequently in such varying ailments as cholecystitis, metastases, renal tumors, gastric ulcers and carcinoma as well as pancreatitis (1–4). Involvement of the entire transverse colon, however, is unusual.

This report concerns two cases of involvement of virtually the total length of the transverse colon by differing processes reaching the colon by differing pathways but producing a strikingly similar roentgen pattern.

Case Reports

Case 1: A 45-year-old male was admitted to the hospital with a 48-hour history of midepigastric, sharp abdominal pain. The patient was a known alcoholic. Examination showed a thin male, extremely diaphoretic, tachypneic and writhing in pain. Blood pressure: 144/60. Temperature: 100.6F. Pulse: 138/min, respirations 30/min. His sclerae were nonicteric. He had diffuse tenderness over his entire abdomen without rebound or rigidity. No definite masses or organomegaly were present. There was a sensation of midepigastric fullness. Rectal examination was negative except for the presence of hematest positive stool. Laboratory findings: white blood count: 12,100/cu mm with slight left shift. Blood urea nitrogen: 57 mg%. Creatinine: 2.1 mg%. Hematocrit: 58%. Serum albumin: 2.8 mg%. Serum amylase: 605 Somogyi units. Urinary diastase: 2830 Somagyi units. Serum calcium: 6.3 mg%. A provisional diagnosis of acute pancreatitis was made and the patient was admitted to the medical service at which time the urinary diastase rose to 3200. He was treated for pancreatitis with antiobiotic, nasogastric suction, IV fluids with resolution of signs and symptoms. Because of persistent pain and occult blood positive stools, a barium enema and GI series were performed (Figs. 1, 1a, 2). Ultrasound examination confirmed a large left upper quadrant cystic mass consistent with a pancreatic pseudocyst and surgical consult was obtained and the patient was evaluated for surgery.

Case 2: A 56-year-old Korean man was admitted to the hospital with a history of several months duration of midabdominal pain and weight loss. On admission, a midabdominal mass was palpated. Physical examination was otherwise unremarkable. Hematocrit: 40.2%. Hemoglobin: 13.8 mg%. White blood count: 13,500/cu

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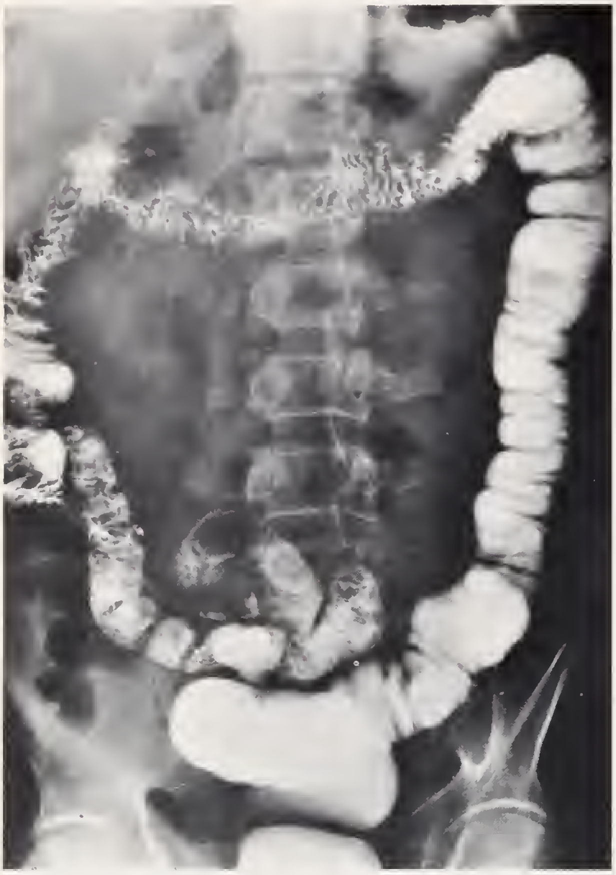

FIG. 1. The transverse colon and hepatic flexure show limitation in distensibility, spasm, thickened somewhat fixed folds which have maintained a spike-like appearance. There is no evidence of mucosal ulceration or destruction nor an extrinsic mass. The soft tissues intervening between the colon and the stomach are not widened. The transverse colon can neither distend nor collapse. Note minimal extrinsic pressure in the region of the splenic flexure.

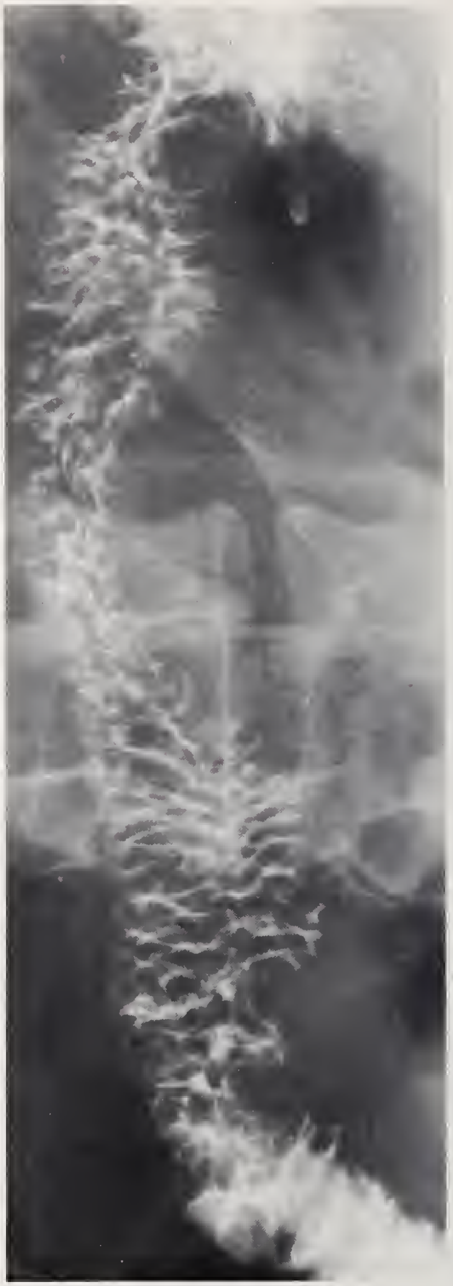

FIG. 1a. Details of mucosal surface showing intact but thickened folds.

mm with a normal differential. His stool was positive for occult blood. A provisional diagnosis of a colonic malignancy was made and a barium enema performed (Figs. 3, 3a). This was followed by an upper gastrointestinal series (Fig. 4). Ultrasound confirmed the presence of a large epigastric solid mass against the anterior abdominal wall. Endoscopy was performed with difficulty but noted the poorly distensible distal antrum and body of the stomach with distortion of the normal rugal pattern and marked reddening of the mucosa. Mucosal brushings showed adenocarcinoma. Liver/spleen scan was normal. To determine the possible further spread of disease, computerized body tomography was performed. The infiltrating antral mass extending to the anterior abdominal wall was noted and had the appearance of carcinoma. There was no further extension of tumor. The patient was prepared for surgery, however, he suffered a cerebral vascular accident to which he shortly succumbed.

Discussion

Both carcinoma and pancreatitis can involve the transverse colon and may, in fact, mimic colonic disease. The recognition of this appearance is, therefore, of some importance.

The colonic manifestations of pancreatitis occur primarily as a result of the spread of pancreatic enzymes along the transverse mesocolon, which

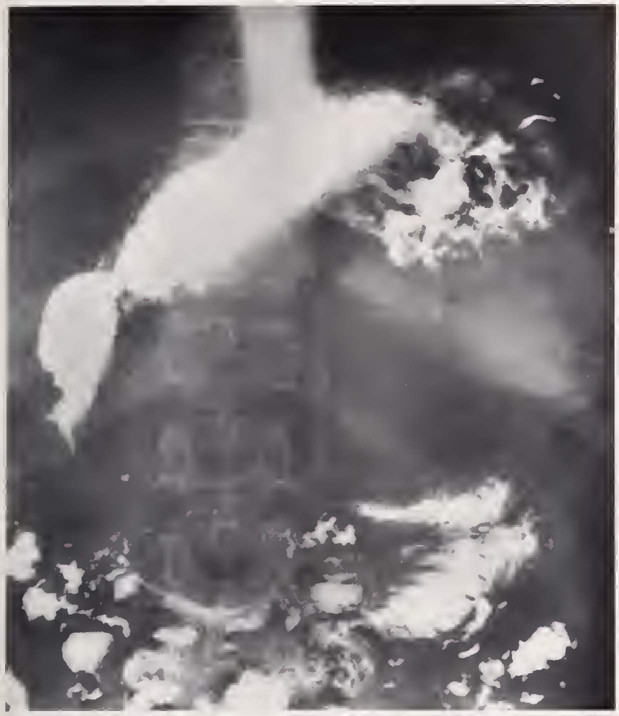

FIG. 2. Large pseudocyst in body and tail of pancreas displacing stomach and small intestine, developing while acute process subsiding.

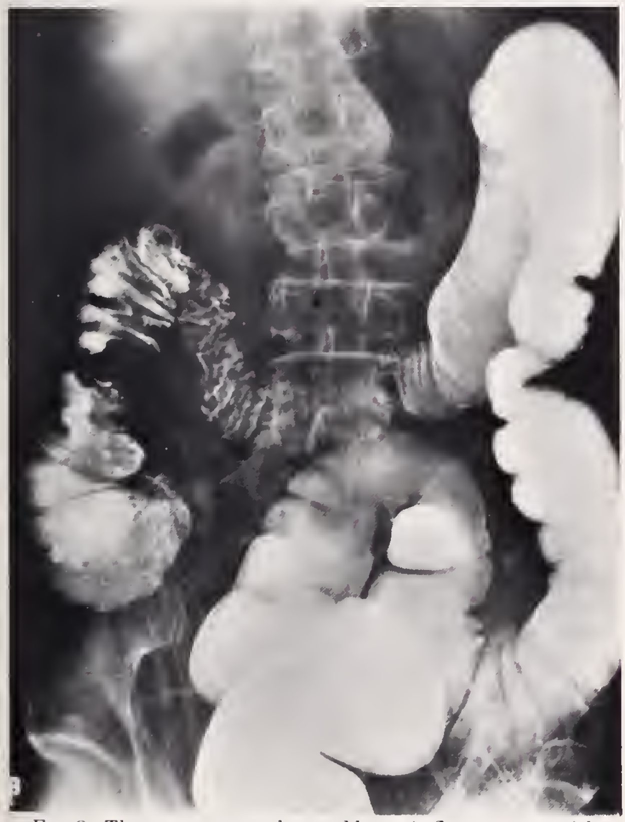

FIG. 3. The transverse colon and hepatic flexure can neither distend nor collapse. The bowel is involved circumferentially. The folds are thickened but do not show a spike-like configuration. The folds are regular, fixed and are symmetrically involved. There is no "pleating" or "tethering" of the folds such as one sees with serosal metastases.

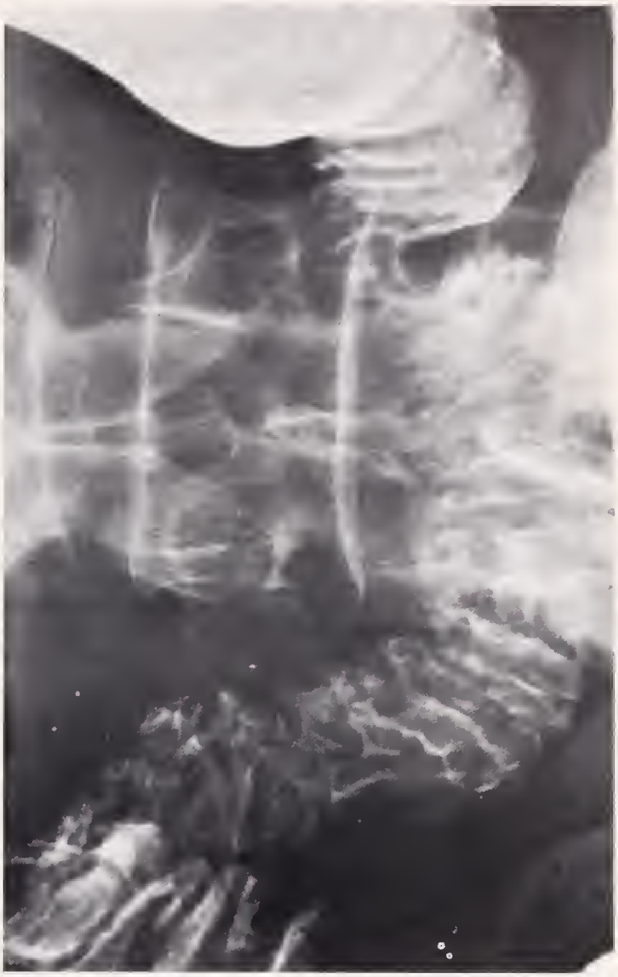

FIG. 3a. Details of mucosal surface showing intact but thickened folds with slight unsharpness and rounding of the edges of the folds in contrast to Figure 1a.

arises from the lower border of the pancreas and inserts along the inferior border of the transverse colon. These changes are usually localized by an irregular spread along the mesenteric planes. Most commonly affected are the regions of the hepatic flexure, where it is enveloped by the beginning of the transverse mesocolon, and the splenic flexure, where the end of the transverse mesocolon, in the region of the tail of the pancreas, inserts at the anatomic splenic flexure of the colon (5). This local response in the transverse colon may be involved at length and circumferentially. Because of the extensive involvement, it can mimic involvement of the transverse colon by carcinoma of the stomach which exerts its effects upon the colon by direct spread via the gastrocolic ligament. Once again, in early disease asymmetrical involvement, namely on the superior border of the colon, will reflect the site of insertion of the gastrocolic ligament. As the disease advances, circumferential involvement ensues. The cancer

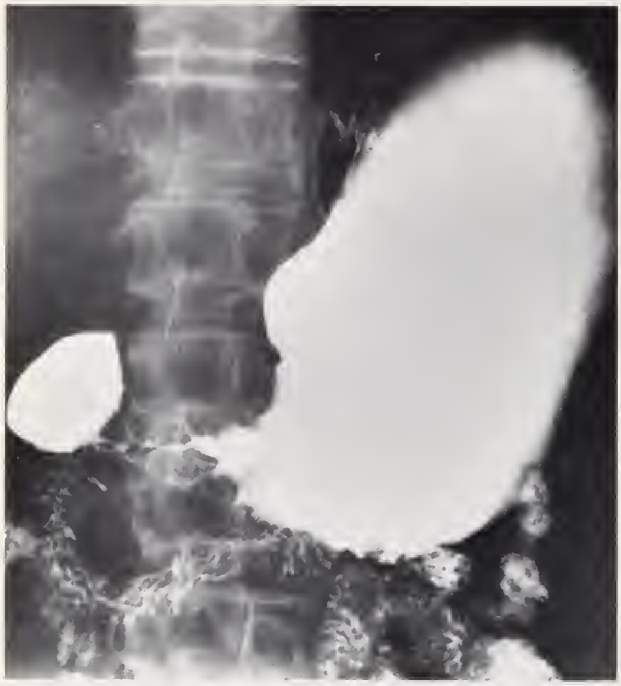

FIG. 4. Ulcerated adenocarcinoma involving the distal stomach.

need not actually invade the colon but produces its alterations by obstruction of the lymphatics and vessels by tumor and associated desmoplastic reaction. As the disease progresses it will spread to involve the bowel wall, the tumor itself now producing focal changes (6, 7).

In both of these cases, the mucosa of the colon has remained intact, making the presence of inflammatory bowel disease an unlikely possibility. However, the absence of obvious extraluminal masses to suggest the extrinsic nature of the process can produce problems in interpretation. Ischemia (8) and intramural hemorrhage (9) may infrequently involve long segments of the transverse colon but the early findings are transitory, either resolving or progressing towards ulceration and necrosis. The clinical picture further supports the diagnosis. Lymphoma (10), particularly involving the mesenteric attachments of the transverse colon could produce this appearance but the length of involvement without nodularity is unusual. The importance of establishing the correct diagnosis from the initial barium enema cannot be too greatly stressed.

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Mucocele of the Appendix: Characteristic CT Findings

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Abstract

A case of mucocele of the appendix with pseudomyxoma peritonei is described. Characteristic computerized tomography (CT) findings of this entity are presented. A brief discussion of the pathogenesis, clinical presentation, radiographic findings, and the differential diagnosis of this lesion is given.

The reported incidence of mucoceles is only 0.2%–0.3% of appendectomy specimens removed at surgery (1, 2, 10). The association of pseudomyxoma peritonei with mucoceles is even less common. The correct diagnosis is rarely made on the basis of clinical or radiographic findings. We describe a case of mucocele of the appendix associated with pseudomyxoma peritonei in which the exact preoperative diagnosis was made with the help of computerized tomography (CT). In reviewing the literature, we did not find any case reports in which the diagnosis was made in this fashion.

Case Report

A 48-year-old man was admitted to Beth Israel Medical Center (BIMC) for repair of an inguinal hernia. He was in general good health and denied any significant abdominal symptoms. Physical examination on admission, apart from the inguinal hernia, was normal. All the preoperative laboratory data and the chest x-ray were unremarkable. During the surgical repair of the inguinal hernia, the hernial sac was found to contain gelatinous material. The hernia was repaired uneventfully and five days later a complete work-up including a barium enema and a CT scan of the abdomen was performed.

The scout film of the abdomen taken prior to the barium enema showed very tiny, faint flecks of calcium in the right side of the abdomen. The barium enema revealed the colon to be intrinsically normal; however, there was medial and anterior displacement of the ascending colon and cecum. The appendix did not fill with barium (Fig. 1).

The CT scan of the abdomen was most useful and precise in outlining the exact nature of the lesion. The CT scan revealed a well encapsulated cystic mass in the right flank. There were numerous flecks of calcium in the wall of the mass. The contents of the cyst were relatively radiolucent with a CT attenuation number of 0.67, consistent with a mixture of fat and fluid. Posterior and caudad to the mass was free fluid demonstrated in the right paracolonic gutter. On the basis of these findings and the gelatinous material found in the hernia sac, a diagnosis of mucocele of the appendix with pseudomyxoma peritonei was made. The diagnosis was confirmed at surgery: a 6.0 × 10 cm retrocecal mucocele of the appendix was found. There was evidence of rupture at the tip of the mucocele with resultant spill of the mucoid substance into the right paracolonic gutter.

Discussion

The concept of mucocele of the appendix has undergone considerable revision in recent years. Originally, the lesion was thought to be caused by an obstruction of the appendiceal lumen with resultant collection of secreted mucoid material proximal to the obstruction (3–6). In a series of recent articles, many authors have stressed the relationship between mucoceles of the appendix

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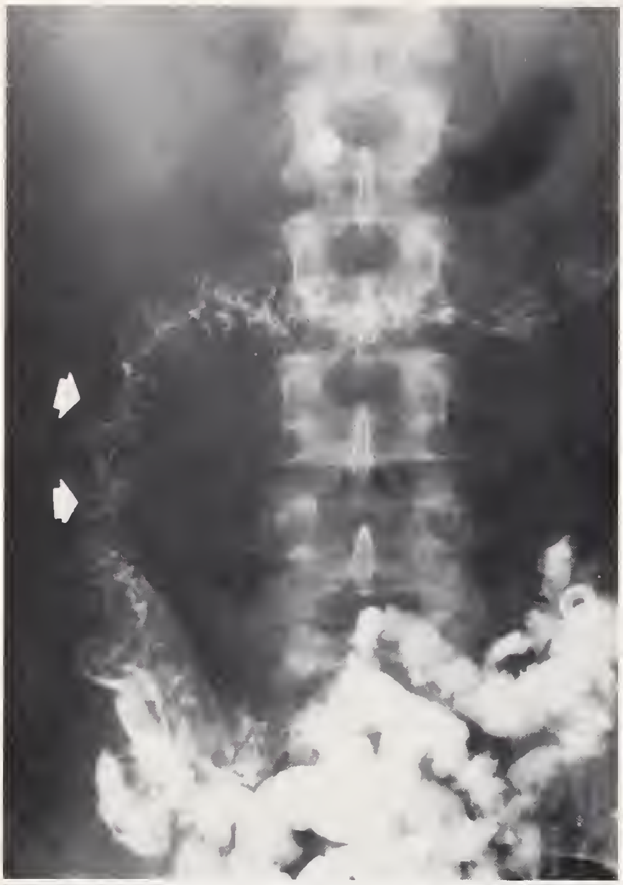

FIG. 1. AP postevacuation film of the Barium enema showing medial displacement of the entire ascending colon and cecum (arrows) away from the lateral abdominal wall.

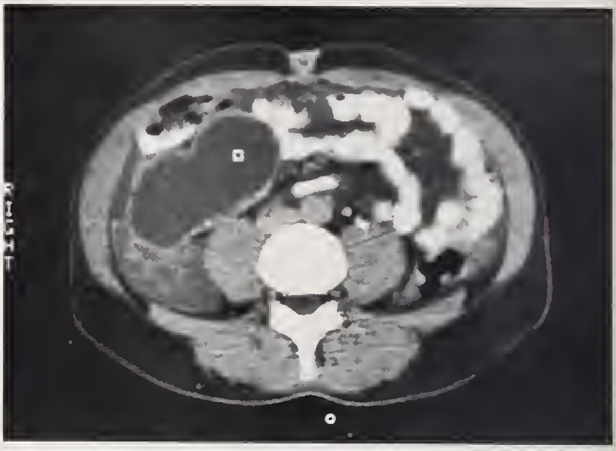

FIG. 2. CT scan through the lower abdomen showing the large well encapsulated structure with numerous calcifications in its postero-medial wall. The CT attenuation was 0.67 (scale − 500 to + 500). Note the anterior and medial displacement of the ascending colon. There is a small amount of peritoneal fluid present posterior and lateral to the cystic mass.

and a range of abnormalities of the epithelial lining of the appendix (2, 7–9).

Based on the published work of Aho (1), Higa (7), Gibbs (8) and Wolff (9), mucoceles can be classified into four groups:

1) simple retention cyst of the appendix in which the epithelium shows atrophic, degenerative changes due to obstruction and distention.

2) mucocele with focal or diffuse mucosal hyperplasia without atypia: the histologic appearance very similar to colonic hyperplastic polyps.

3) mucinous cystadenoma of the appendix exhibiting some epithelial atypia, morphology very similar to colonic villous tumors and adenomatous polyps.

4) mucinous cystadenocarcinoma of the appendix with evidence of stromal invasion by glands.

A feature common to all four groups is the secretion of a mucoid material which tends to pool within the appendix due to the inherent anatomic structure of the appendix.

The clinical behavior of the first three groups is completely benign, surgical removal of the appendix is curative and there is no recurrence of the mucoid material in the peritoneal cavity (2, 9). The adenocarcinomas of the appendix behave similarly to other invasive carcinomas, the five-year survival in one series of patients was only 25% (1).

The pathogenesis of pseudomyxoma peritonei has received some attention in the literature (9). Two theories of its formation have been proposed: the first is that tumor cells implant on the peritoneum and actively secrete the mucoid material. The second theory is that extravasated mucin irritates the peritoneum, causing metaplasia of the mesothelial cells which in turn produce mucin. Shanks (11) has suggested that both mechanisms may be operative in cases of pseudomyxoma peritonei.

The clinical picture is varied and nonspecific. In a series of 45 cases, described by Parson (12), 20% of patients were asymptomatic and the mucocele was an incidental finding during laparotomy. Thirty percent of patients with mucoceles of the appendix presented with a chronic history of right lower quadrant abdominal pain and discomfort; 27% of cases presented with symptoms of acute appendicitis. In patients with pseudomyxoma peritonei, the presenting complaint was increasing abdominal girth; rarely, as in our case, gelatinous material will be found in the hernial sac during a herniorrhaphy (12).

The radiographic findings in patients with mucocele are also nonspecific, although a combination of findings may lead to the correct diagnosis. The finding most frequently cited is the presence of ring-shaped or punctate calcifications in the right lower quadrant of the abdomen associated with an extrinsic or intramural type

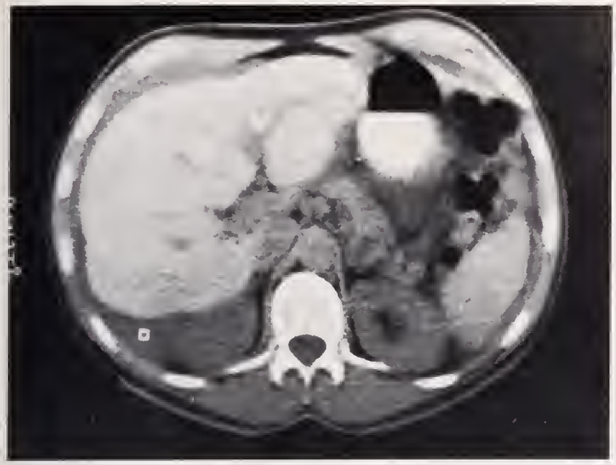

FIG. 3. CT scan of upper abdomen (at level of liver and kidneys) shows the characteristic appearance of peritoneal fluid surrounding the liver.

mass effect on the barium-filled cecum (1, 7, 12). The appendix is usually not opacified during the barium enema.

In our patient, in addition to the fine punctate calcifications and the presence of an extrinsic extra-colonic mass, the CT findings were very specific. The presence on CT scans of a well encapsulated mass with punctate calcifications in the wall and with low attenuation contents inside the mass enabled us to make a precise diagnosis preoperatively. The low attenuation of the cyst contents as well as of the peritoneal fluid is thought to be typical of the mucoid contents of the mucocele and the pseudomyxoma peritonei.

Differential Diagnosis

The differential diagnosis includes other calcified lesions in the right lower quadrant such as mucin producing adenocarcinoma of the cecum or the ovary. Calcified uterine fibroids can mimic these calcifications. Rarely, hemangioma of the gastrointestinal tract may present with multiple calcifications due to the presence of phleboliths. Ring calcifications are also produced by vascular malformations and aneurysms, enteroliths, calcified hematomas, old abscesses, echinococcus cysts, etc. Any extrinsic mass can indent the cecum on a barium enema; also to be considered are intramural tumors such as lipomas, leimyomas, etc.

None of these lesions, however, will present the characteristic CT findings shown in our case, which we believe to be specific for mucocele of the appendix.

The CT differential diagnosis should also include other "fatty" masses such as retroperitoneal lipoma and a pelvic dermoid cyst. The retroperitoneal lipomas usually lack a well defined capsule and extend diffusely into many planes of the retroperitoneum. Dermoid cysts will not show a constant relationship to the cecum on a barium enema.

Summary

A case of mucocele of the appendix and pseudomyxoma peritonei is described which in our opinion presents characteristic CT scan findings. To our knowledge, this is the first case described in which the CT scan findings enabled one to make a specific preoperative diagnosis.

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Benign Pancreatic Cystadenoma

Yves Joseph, M.D., Ruben Pochaczevsky, M.D., and Ulrick Vieux, M.D.

A cystadenoma of the pancreas is a rarely occurring cystic neoplasm most commonly situated in the tail or body of the gland. The lesion must be distinguished from a pseudocyst or adenocarcinoma of the pancreas. The case presented demonstrates many of the characteristic features of cystadenoma as well as other changes that are somewhat unusual.

Case Report

A 60-year-old Hispanic female, with known diabetes for ten years, requiring 25U of NPH insulin subcutaneously daily, was admitted to Elmhurst Hospital because of jaundice, mid epigastric abdominal pain radiating to the back, dark urine for three days and alcoholic stools for one month. She also noted a 2 kilo weight loss in one week with an accompanying loss of appetite and nausea.

There was no vomiting, hematemesis, constipation or fever. She had no history of parasites, ethanol abuse or abdominal trauma and had not travelled recently. With the exception of a cholecystectomy 25 years prior to admission and hysterectomy 20 years prior, her medical history was unremarkable.

Physical examination revealed an obviously jaundiced female in no acute distress with a right sided, firm, nontender abdominal mass. Two surgical abdominal scars from the previous cholecystectomy and hysterectomy were noted. Her blood pressure and pulse rate were normal. Respiratory rate was 10/min and regular. All laboratory data were noncontributory except for a bilirubin of 8.8 values and minimal transaminase elevation.

A plain film of the abdomen disclosed a large mass containing curvilinear calcifications that occupied most of the right upper quadrant, the mass with extended towards the mid upper abdomen and down to the mid L5 level (Fig. 1).

An IVP with nephrotomography (Fig. 2) revealed normal renal contours and collecting systems. The previously described calcified mass was lateral to the lower pole of the right kidney. Several tomographic cuts demonstrated multiple radiolucencies within the mass. An upper gastrointestinal series (Fig. 3) showed that the mass was situated in the head of the pancreas.

Angiographic studies defined a hypervascular mass involving the head of the pancreas (Fig. 4). Ultrasonography described a complex mass with a large cystic component in the right upper quadrant (Fig. 5).

The patient underwent an exploratory laparotomy during which her blood pressure progressively fell and her pulse rate became rapid and weak. She left the operating room in a state of shock. Her vital signs continued to be unstable despite transfusions of fresh blood and packed cells and she expired.

The surgical specimen included segments of the stomach and duodenum as well as the pancreatic mass. The latter measured 12 cms in diameter and consisted of numerous cystic areas containing light brown viscid fluid. Several cysts were separated by firm fibrous tissue with a calcific consistency. The pathologic diagnosis was that of a cystadenoma of the pancreas.

Discussion

Pancreatic cystadenoma is a rare cystic tumor arising from pancreatic acinar epithelium. It is a slow growing neoplasm whose symptoms have usually been present for many years before detection. In order of frequency, the symptoms usually include abdominal pain, weight loss, belching, excessive gas, nausea, vomiting, diarrhea, weakness and fatigue, bleeding, jaundice and dyspnea although some patients may be entirely asymptomatic (6).

Among the clinical findings, an abdominal mass is the most commonly encountered. This tumor occurs at an earlier age than pancreatic carcinoma. It has a peak incidence between the fourth and sixth decades of life, although cases have been reported as early as the sixteenth month of life (18). Its sex predilection is striking,

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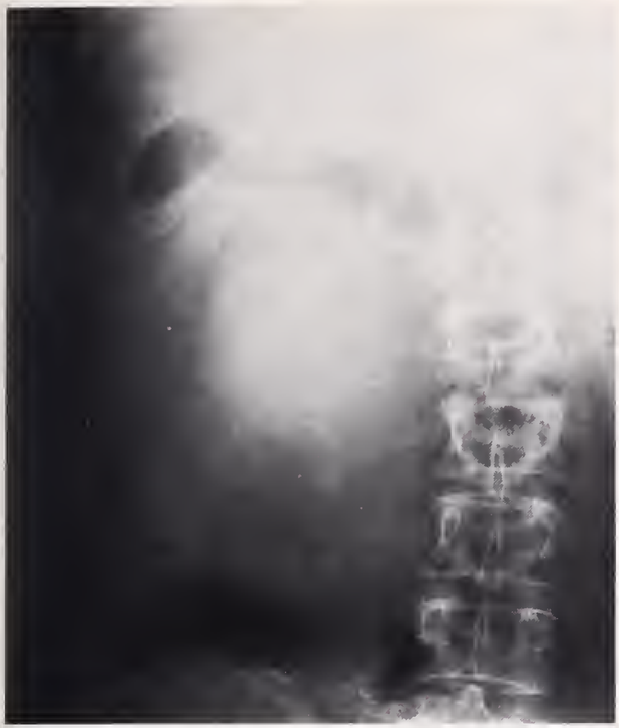

FIG. 1. The plain film of the abdomen shows a large mass in the right upper quadrant with "spokewheel" calcifications.

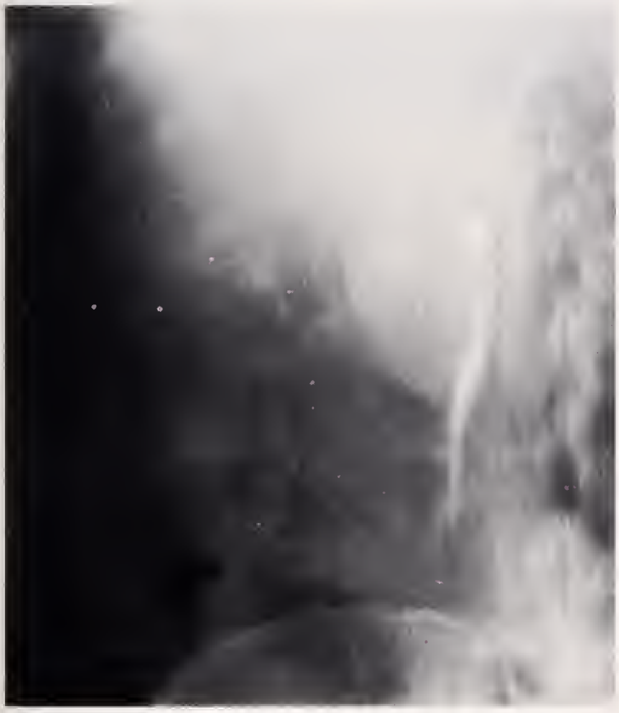

FIG. 2. Nephrotomographic cut in the right posterior oblique projection. The contour of the right kidney is well defined. The mass is anterolateral to the lower border of the kidney and contains multiple lucencies.

with a ratio of 9:1 in favor of females. There are reported associations of cystadenoma with diabetes and/or cholelithiasis. In our case, the patient was a known diabetic for ten years and underwent a cholecystectomy for cholilithiasis 25 years previously.

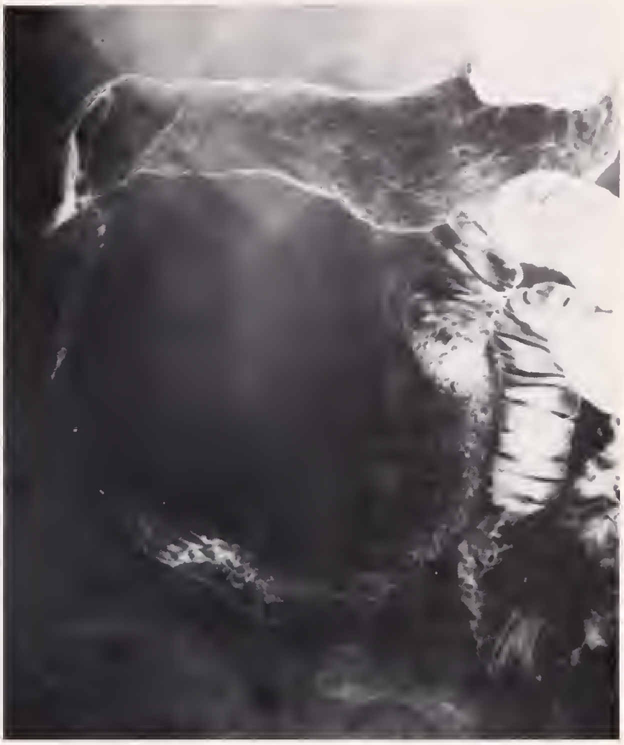

FIG. 3. AP view shows a dramatically widened duodenal sweep with a stretching and "ironing-out" of its mucosa. The gastric antrum is displaced upward.

The majority of these tumors are located in the body and tail of the pancreas. They are never found in aberrant pancreatic tissue (7). The lesion ordinarily does not reach the size encountered in the pancreatic pseudocyst. The outer surface appears honeycombed because of the numerous closely packed cysts. The cellular structure varies greatly and pathologists may differ in classifying cystadenomata. Two histologic types have been described: mucous and serous cystadenoma (5, 6). The mucous type appears grossly unilocular and has a tendency to be malignant (6) while the serous type is composed of multiple cystic components and is usually benign.

The current case is representative not only of a rare lesion but of an unusually large sized tumor that occupied most of the right upper quadrant and had roentgenographically discernible calcifications within it. Because of its position (Fig. 1), a liver mass could not be excluded. The upper gastrointestinal series, however, (Fig. 3) revealed a widened duodenal sweep which helped establish the location of the mass in the head of the pancreas.

Contrast studies demonstrated radiolucent highlights within the mass consistent with areas

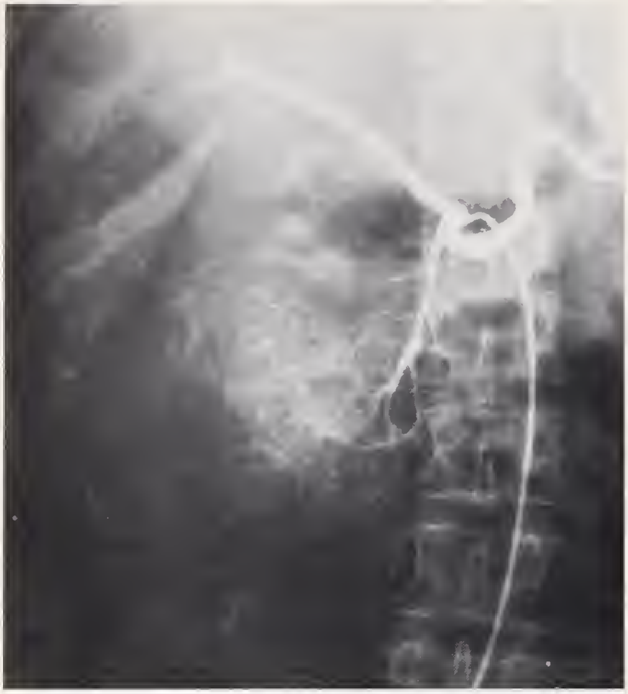

FIG. 4A. A splenic artery injection resulted in hepatic artery reflux. The dorsal pancreatic artery is hypertrophied feeding multiple abnormal vessels in the head of the pancreas.

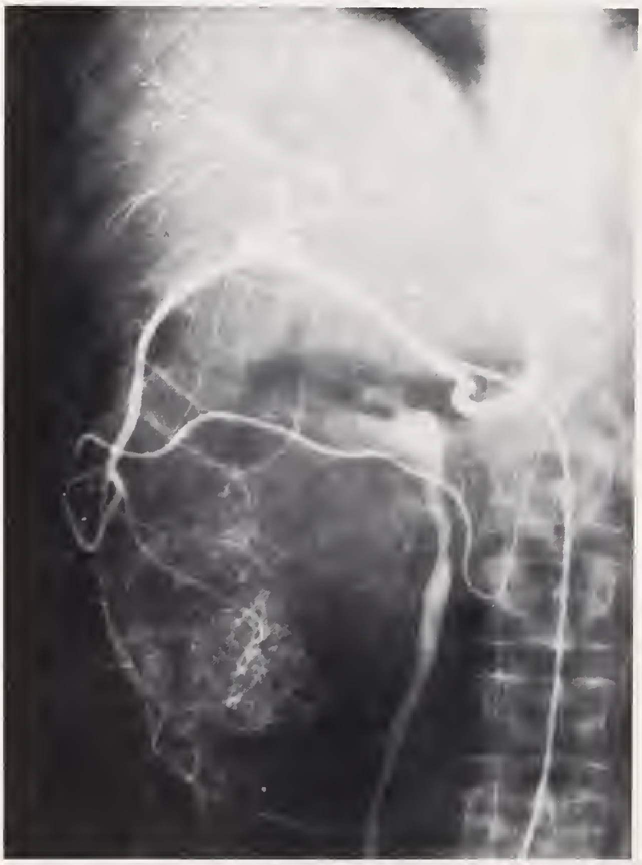

FIG. 4B. Selective hepatic arteriography. Note the common hepatic artery is stretched over a vascular pancreatic mass, and the gastroduodenal artery is markedly displaced along the course of the descending duodenum producing multiple branches that supply the tumor.

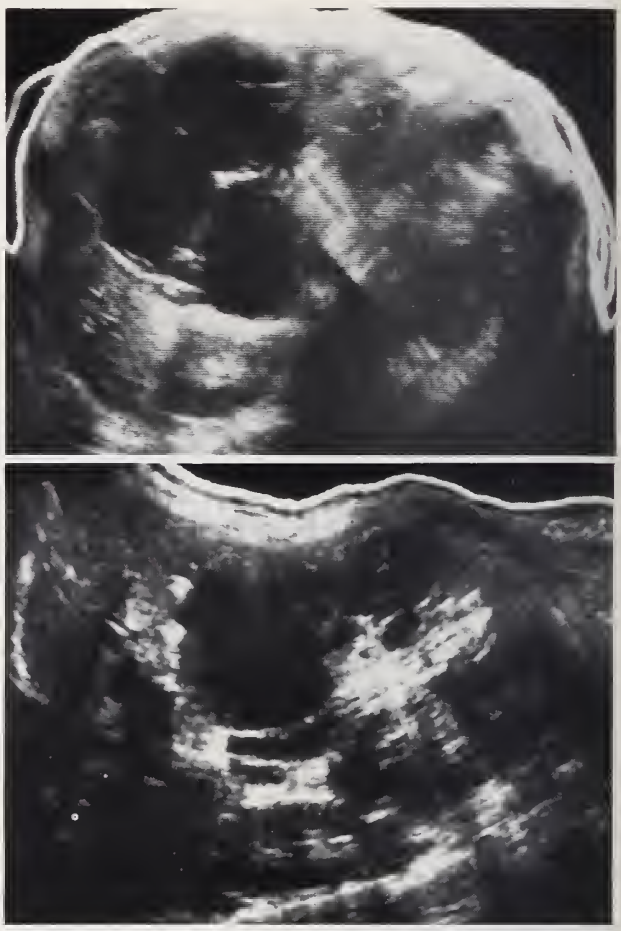

FIG. 5A & 5B. Transverse ultrasonographic cut taken at (A) 8 cms above the umbilicus and (B) a longitudinal cut 11 cms to the right of the midline reveal a huge mass occupying most of the right upper quadrant with large cystic components separated by septa, as well as solid masses.

of cyst formation (Fig. 2). Angiograms (Figs. 4A, 4B) revealed an important feature of these neoplasms—their high degree of vascularity which differentiates this tumor from a pseudocyst or adenocarcinoma of the pancreas. Angiographic findings described a displacement of major vessels, presence of large feeding arteries, accumulation of contrast medium within the tumor associated pooling of contrast medium and numerous pathologic vessels. Although hypervascularity appears to be a prominent radiologic feature, avascular cystadenomas have also been reported (4, 6, 14). The enlargement of the dorsal pancreatic artery confirmed the location of the tumor within the head of the pancreas. The differential diagnosis between cystadenoma and nonfunctioning islet cell adenoma may be difficult since both are vascular tumors. The hypervascular cystadenomas are more likely to have severe arteriovenous shunting, higher flow and increased venous return.

There have been few ultrasonographically documented cases of pancreatic cystadenoma (11). They emphasize the delineation of sonolucent cystic structures with septa formation within the tumor. The present case also documents the presence of a characteristically complex mass with a predominence of cystic components and septa formation within it (Figs. 5A, 5B).

Ten percent of the tumors show roentgen evidence of calcification (1, 8, 10, 13, 14). Deposition occurs in the cyst wall and, when present, varies from a few small, irregular particles to quantities that form a radiating curvilinear appearance following the septae as noted in our patient.

Summary

A case of a large cystadenoma of the head of the pancreas is described. Its clinical, plain radiographic, angiographic and ultrasonographic findings are presented. Its characteristic hypervascularity as seen on angiography and its cystic ultrasonographic features are emphasized.

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Radiology of Fish Foreign Bodies in the Hypopharynx and Cervical Esophagus

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The lodging of fish bone foreign bodies in the hypopharynx and upper esophagus is frequently attended by such severe clinical symptoms and complications as to make early recognition and localization of paramount importance. Exact localization of the foreign body greatly facilitates its endoscopic removal and diminishes the likelihood of operative complications. It is, therefore, natural that radiographic examination has long played a role in the diagnosis of these foreign bodies. However, a considerable difference in success in directly visualizing these bones on the roentgenograms has been reported by various authors. For this reason an investigation of the value of radiographic examination in the diagnosis of the fish bone foreign bodies was undertaken.

The study is divided into two sections: 1) a review of clinical cases, that was done in association with Dr. Joseph L. Goldman and 2) a radiographic study of numerous different fish bones placed in a suitable water phantom.

Inadequacies of the early radiographic techniques resulted in frequent false negative reports in cases of suspected fish bone foreign bodies in the upper esophagus. This led to a doubt about the efficacy of radiography in diagnosing these poorly calcified bones. However, with improved equipment permitting fast exposures and fine focal spots, direct recognition of these bones has become much more frequent (1). Recently, xeroradiography has been reported to be superior to conventional radiography in visualizing the low density fish bones as well as nonopaque foreign bodies (2, 3). At this time also, computerized tomography (CT) is under evaluation for soft tissue foreign bodies (4). There is little doubt, nevertheless, that some thin fish "bones"–essentially cartilagenous slivers with only minimal amounts of calcium–cannot be visualized directly.

Opaque foreign bodies situated in the hypopharynx and cervical esophagus are, obviously, more satisfactorily visualized than those lodging in the thoracic esophagus. The comparatively large volume of the thorax, the multiplicity of soft tissue structures in the mediastinum, and the numerous overlying bone shadows usually make recognition of the poorly calcified foreign bodies exceedingly difficult. This difficulty is greatly diminished in the neck, where the volume of tissue is small and the soft tissue densities are present in relatively simple array on the lateral radiograph. Most esophageal foreign bodies lodge in the cervical region at or just above the sternal notch (1, 6–8, 15) where the lumen is narrowest at the pharyngoesophageal junction. Thus, x-ray examination of the cervical region appears warranted in cases of suspected foreign bodies, particularly if there are complaints referable to the neck.

Comparatively little has been written and considerable difference of opinion exists concerning the success of direct radiographic visualization of fish bone foreign bodies. Many of the radiologists writing before the mid-forties reported inadequate visualization of the bones. Thereafter, refinement of roentgenographic techniques permitted foreign bodies to be seen more readily. The technique of Skarby (7) and Laurell (9) is essentially the same as that used today. It employs a) the smallest possible field by sharp coning, b) a fine focus tube, c) a large (30 cm) object-film distance to diminish scattering by geographic effect, d) the largest practical target-film distance (1.5–2.0 m) so that the magnification and distortion factor of the large object-film distance can be overcome, e) high voltage (90–115 KVP) to use the primary beam and diminish the exposure time, and f) shortest exposure time practical.

Regardless of the efficacy of the roentgenogram to visualize fish bones directly, two valuable, indirect findings have been reported by various investigators (7, 8, 10). These are local swelling in the prevertebral area and the presence of abnor-

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mal gas shadows or bubbles in this area, indicating perforation of the esophageal wall and/or gas-forming infection. Brown (8) states that whenever the diameter of the prevertebral soft tissues exceeds that of the adjacent cervical vertebra or adjacent trachea, a foreign body should be suspected.

Several investigators have reported on the use of contrast material to aid localization of nonopaque foreign bodies in the esophagus. Wilson (11) had the patients swallow barium-soaked cotton or wool pledgets. He hoped that the pledgets would become caught and remain fixed on the foreign body, enabling the foreign body's position to be determined. This method has been reported as unsatisfactory by several observers (7, 12) and is not in general use. Capsules filled with bismuth or barium were employed with the expectation that their descent down the esophagus would be arrested by the foreign body. Again, this method has not proved successful except for the largest foreign bodies and is currently not in general use. Most commonly employed at present are barium pastes or suspensions of various thickness.

Carlsund (5) and Haglund et al (1) describe a simple and excellent technique. A rather thick barium mixture is first swallowed and a radiograph made. The patient then drinks several mouthfuls of water that wash away all the barium on the normal esophageal mucosa. Small amounts of barium often cling to any foreign body present, however, and thus outline it on a second radiograph made after the water drink. Fluoroscopy during the barium swallow also may aid in showing esophageal spasm and delay at the foreign body site.

Caution in the use of barium to identify an esophageal foreign body has been advocated by some. Utrata (13) suggests that the barium can coat the foreign body, obscure it during esophagoscopy, and thus complicate its successful removal. Brown (8) advises that it should be reserved only for esophageal foreign body cases in which the plain films are negative.

Materials and Methods

The present investigation is divided into two sections:

(1) Clinical study of fish bone foreign body cases.
(2) Experiments concerning the radioopacity of various fish bones.

The clinical material includes a group of 56 cases with suspected fish bone foreign bodies in the esophagus that were studied radiographically at The Mount Sinai Hospital in New York City.

The age and sex distributions of the cases are shown in Table I. The preponderance of females is clearly evident.

Of the 56 cases admitted to the hospital, a fish bone was demonstrated at esophagoscopy or operation in 40 instances. The bone was found in the cricopharyngeus region in 17 cases. In 22 other cases, it was seen low in the neck lodged just below the cricopharyngeus but above the thoracic inlet, and in one case it was in the thorax.

Direct visualization of the fish bones themselves was obtained radiographically in 30 cases (75%) (Table II). The visualized bones differed considerably in size, shape and appearance. They were usually of linear or band-like thickness; in the latter instances, the bones either were fairly large or were flat bones presenting "on end" (Fig. 1). Most often they were of uniform density, but varied from faint to marked opacity. Occasionally, the bones were punctate in appearance and resembled incompletely calcified laryngeal cartilages, especially when they were present in the hypopharynx at or above the cricopharyngeus muscle. When they were lodged in the cervical esophagus below the larynx, they could be seen in the retrotracheal soft tissues and recognition made with greater ease.

The occurrence of the two important indirect radiographic signs, prevertebral widening and gas bubbles in the prevertebral tissues, was also studied in the 40 proven cases. Recognition of

TABLE I

Age	Male	Female
0–20	1	2
21–40	3	12
41–60	6	20
61–	1	11
	11	45

TABLE II

Radiographic Findings in 40 Proven Cases of Esophageal Fish Bone Foreign Bodies

X-ray Findings		No. Cases
A. Fish bone directly visualized		30
1. No prevertebral widening	18	
2. With prevertebral widening	12	
3. Gas in the soft tissues	5	
B. Fish bone not visualized		10
No prevertebral widening or gas (X-ray negative)	5	
2. Prevertebral widening present	5	
3. Gas in soft tissues	1	

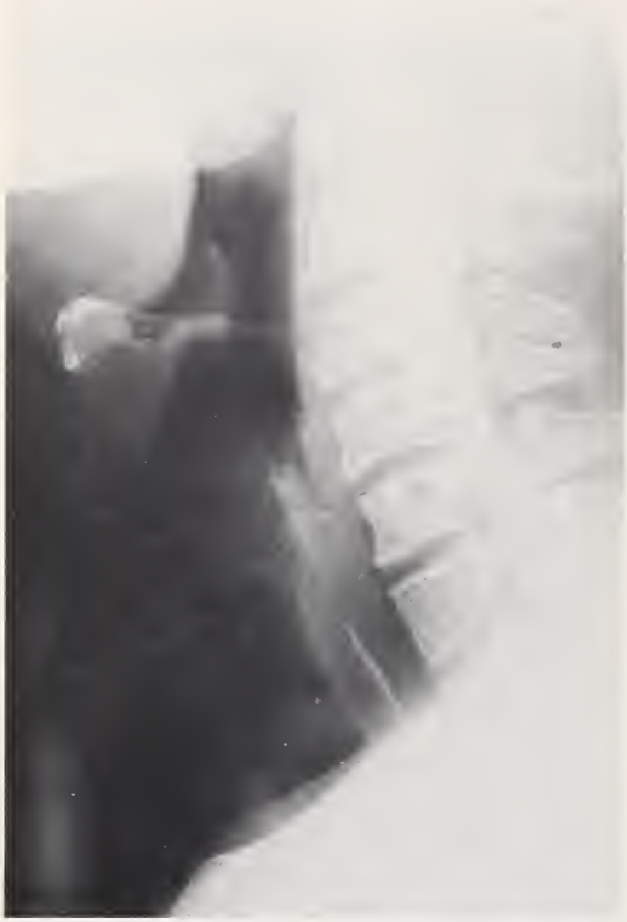

FIG. 1A. Band-like density of flat haddock bone seen "on end" in upper end of esophagus. No prevertebral soft tissue swelling.

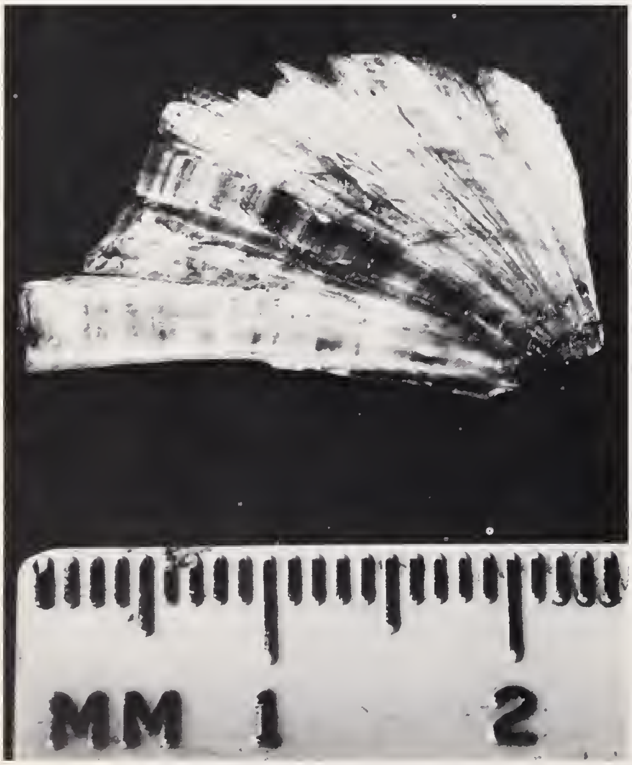

FIG. 1B. The bone that was removed.

prevertebral soft tissue widening usually was accomplished with comparative ease. Normally, the prevertebral space is narrow in the hypopharynx and behind the larynx, measuring up to 0.8 cm in width. At the C5-C6 level, the esophagus begins and the space increases in width. Thus, in the inferior portion of the neck, the prevertebral space measures up to 1.5 cm in thickness but usually no wider than the body of the adjacent cervical vertebra. A local soft tissue bulge is often seen at the esophageal opening, not to be mistaken for abnormal widening. When widening associated with the presence of fish bones occurred above the level of the larynx, the soft tissue space became as thick as or thicker than that of the esophageal region (Fig. 2). When this swelling occurred at the esophageal level, the prevertebral space became wider than the adjacent cervical vertebral body (Figs. 3, 7). The zone of widening was usually not sharply circumscribed. Within it, the fish bone or abnormal gas shadows frequently were observed. If the widening extended below the thoracic inlet, mediastinitis could be correctly inferred. The gaseous shadows were usually multiple, irregularly globular or linear shape, and grouped together within the widened prevertebral area (Figs. 2, 3). They were often seen about the fish bone. Occasionally, trapped air in the upper esophagus offered difficulty in differentiation. However, this normal finding was usually a single elongated shadow which conformed to the outline of the esophagus.

From Table II it is seen that in 17 or the 40 proven cases (42.5%) there was local prevertebral soft tissue widening in the cervical region. Further, whenever abnormal gas bubbles were seen in the prevertebral soft tissues the prevertebral space was also widened (Figs. 2, 3). In only five of the 40 cases were the radiographic studies completely unrevealing.

There were 16 patients whose clinical syndrome following ingestion of fish warranted hospitalization but in whom a fish bone was not demonstrated during esophagoscopy or operation. The x-ray findings in these 16 cases were as follows:

EXTRACT 1

X-ray of neck normal	....	9 cases
Fish bone visualized	....	2 cases
Only indirect findings present	....	5 cases
a) Prevertebral widening alone	....	2
b) Prevertebral widening plus gas	....	3

The significance of prevertebral widening and gas in the retroesophageal soft tissues was studied

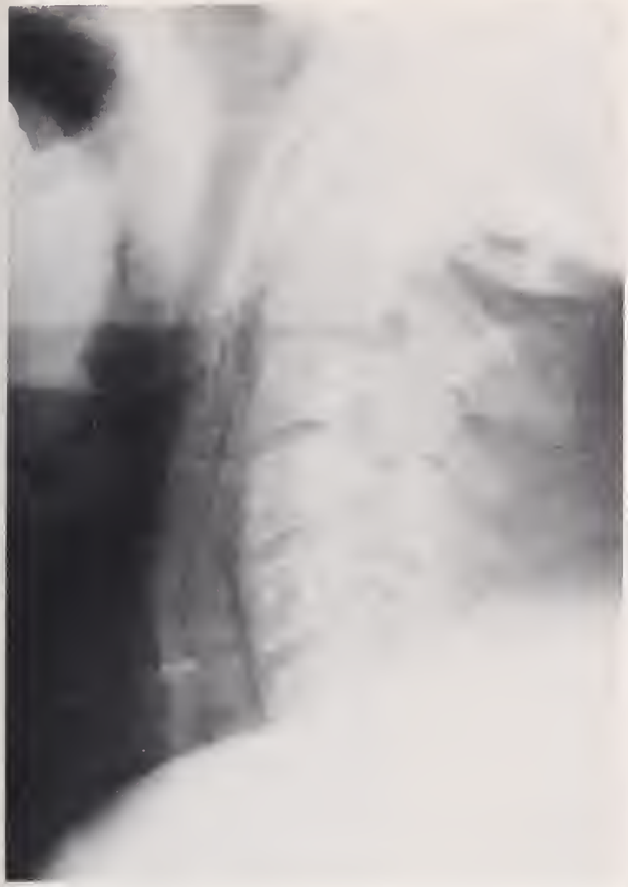

FIG. 2. Small fish bone in prevertebral space just above thoracic inlet. Prevertebral gas in irregular linear formation. Moderate soft tissue swelling in hypopharynx above cricoid cartilage.

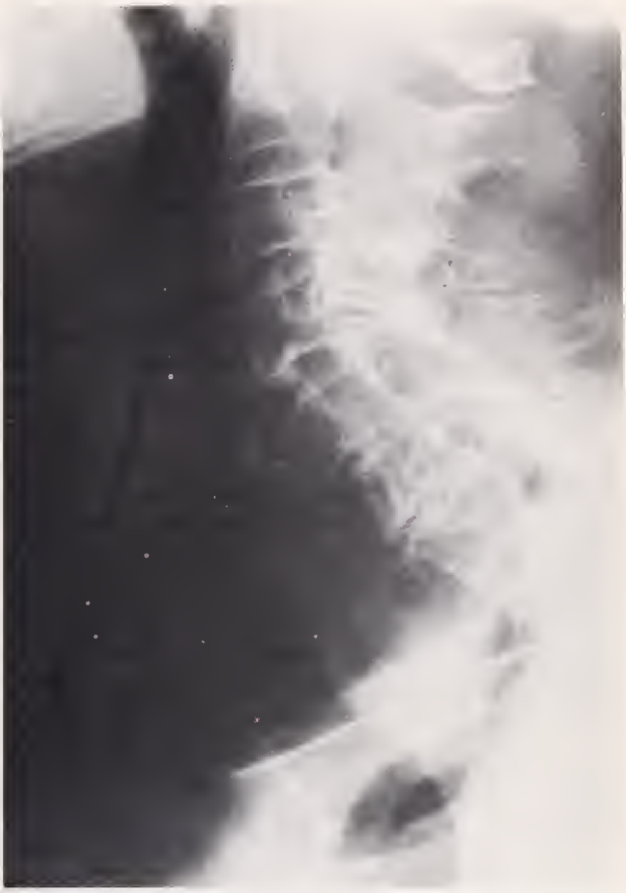

FIG. 3. Prevertebral abscess in neck as a result of a fish bone foreign body penetration. Note the irregular gas bubbles and marked widening of the prevertebral space.

next. Of the 56 cases, prevertebral widening was observed in 21 instances (37.5%). Of these 21 cases, a fish bone was seen on esophagoscopy in 16 patients and visualized roentgenographically 12 times. Widening often occurred early (Table III). In three cases it was observed within 12 hours after the bone became lodged and, in one case, was noted within three hours.

In addition, the longer the period of sojourn, the greater the likelihood of widening.

Serious complications attributable to the fish bones were noted in ten of the 56 patients (18%). There were four cases of periesophageal abscess, three cases of mediastinitis and three instances of esophageal perforation. In each case there was highly significant radiographic findings. The bone itself was visualized six times, prevertebral widening was present in every instance, and in nine of the ten cases, gas shadows were observed in the widened prevertebral space.

TABLE III

Prevertebral Widening and Period of Sojourn

Duration of Sojourn	No. Cases with Widening
Up to 12 hours	3
12 to 24 hours	4
24 to 48 hours	2
Over 2 days	9
Unknown	3

Investigations Concerning Radio-opacity of Fish Bones

Rib bones of varying thickness and size were removed from 21 different species of fish for this study. Usually, more than one bone from each type of fish was radiographed, and bones from uncooked and cooked fish were employed. After the thickness and shape of the bones were noted, the specimens were radiographed in a phantom consisting of a hollow plastic model simulating the lower face, neck, and thoracic inlet (Fig. 4). The neck portion measured 10 cm in diameter. A plastic cylinder, 1.5 cm in diameter, was placed in the anterior portion of the hollow shell to represent the laryngotracheal airway. The phantom was then filled with water except for the cylindrical

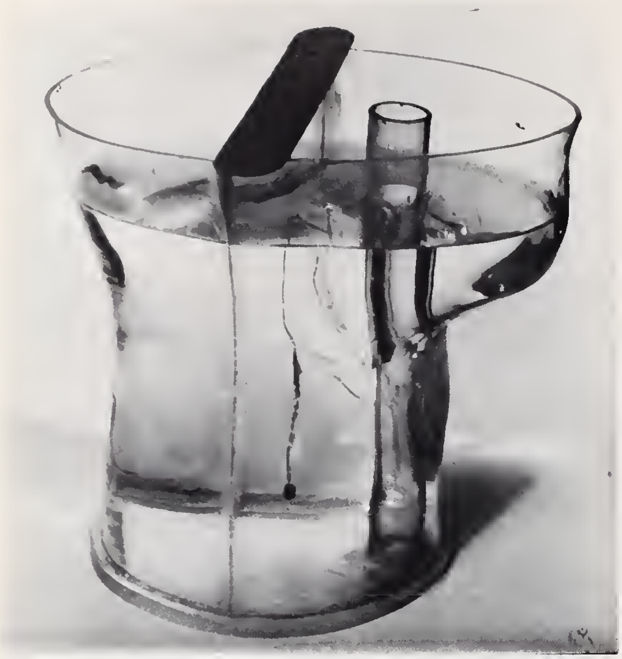

FIG. 4. Cervical phantom. Fish bones were attached to the cotton string suspended from the tongue depressor straddling top of phantom.

airway. The size and shape of the cervical container and the use of water as the phantom material resulted in an excellent simulation of the cervical region for radiographic purpose. The bones were attached by scotch tape to completely radiolucent cotton threads and suspended in the water behind the pseudolaryngotracheal airway or within the air column itself. In most instances, x-rays were taken with the bones both in water and the air column to determine any differences in radiographic appearance. Different x-ray techniques were tested; and the effect of over-exposure, optimal exposure and under exposure techniques on the radiographic demonstrability of the fish bones was noted.

The results of the experiments on the radiographic visibility of the various bones x-rayed in phantoms are summarized in Table IV. In general, the bones of each type of fish were of consistent radiopacity. In only two instances, bluefish and mackerel, did several specimens of the same species provide a noteworthy difference in visualization, although here too the radiographic variations were not marked. Usually, the thicker and larger a bone in a given species the better it was demonstrated. Thin bones of some species were better visualized, however, than thicker bones from other fish. The visibility appeared to depend upon the amount of calcific salts present rather than the size of the bone.

In about half the trials, the fish were cooked prior to utilizing their bones. There was no difference in the radiographic visibility of the cooked and uncooked bones. The speculation that cooking of the fish might make faintly opaque bones completely radiolucent (14) was not substantiated by the present investigation. As might be expected from the high percentage of direct visualization in

TABLE IV

Experimental Radiopacity of Fish Bones in Phantom X-ray Appearance

Fish	No. Bones X-rayed	Definitely Diagnostic	Visible but Poorly Defined	Invisible
Bass	2	2		
Bluefish	4	3		1
Butterfish	3			3
Codfish	5	5		
Flounder	3	3		
Fluke	2	2		
Fresh Salmon	4	4		
Gray Sole	2	2		
Haddock	2	2		
Halibut	4	4		
Mackerel	4	1		3
Pompano	5		2	3
Porgie	3	3		
Red Snapper	2	2		
Sea Bass	2	2		
Smelt	1	1		
Smoked Salmon	2	2		
Striped Bass	2	2		
Trout	3		2	1
White Perch	2	2		
Yellow Pike	3	3		

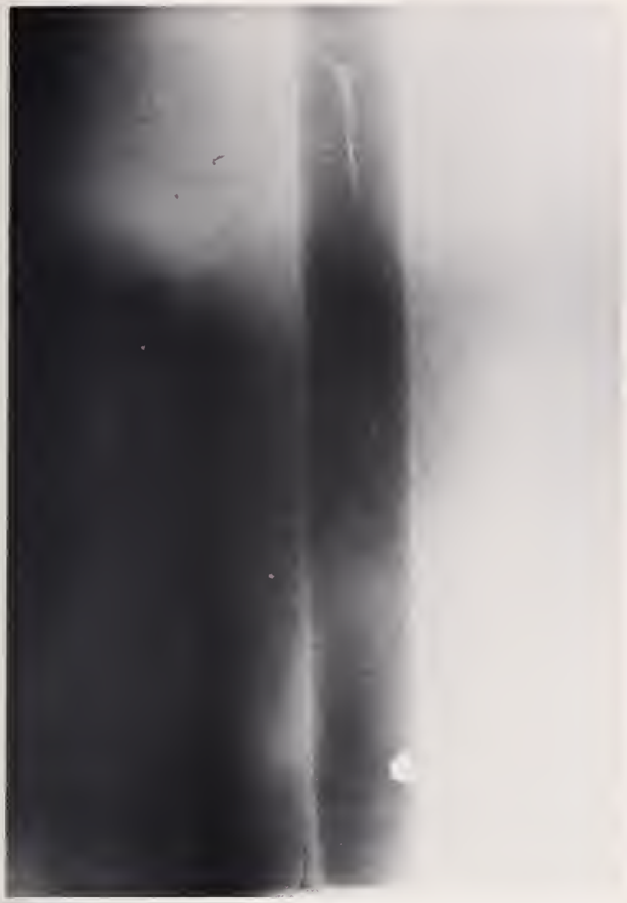

FIG. 5A. Two fish bones in air column of phantom. Clearly visible.

FIG. 5B. Same two bones in the water. Upper bone barely visible.

the clinical study, most of the bones were clearly visible when x-rayed in phantom. However, the bones of several species could not be seen when in the water of the phantom. All the bones, regardless of their size or density, were better visualized when radiographed in the air-column than when situated in the water (Fig. 5).

A technique was found to affect visualization of the fish bones in phantom significantly. The best results were obtained with a small focal spot (1 sq mm) the smallest practicable field size and a radiograph which was slightly dark. The latter was distinctly preferable to a light film. In several instances (bluefish, fresh salmon, smoked salmon) a bone which was not visible on an under-exposed or considerably over-exposed radiograph became clearly apparent on a slightly dark film. Time of exposure played no significant role in these studies since there was no motion in the phantom.

In the case of flat bones, the presentation of the bone was important in achieving visibility. In one experiment, a rather dense flat bone from halibut was x-rayed "en face" while in the phantom. On the radiograph its apparent density was considerably less than those of three other halibut bones not x-rayed "en face." In another instance, a radiograph of the neck showed a dense, almost linear foreign body in the upper esophagus. Upon removal, it was found to be a large fan-shaped gill bone of a haddock (Fig. 1). Roentgenographs of this bone in the cervical phantom were then made. When the bone was filmed "on end," its appearance greatly resembled that seen in the patient's radiograph. When arrayed "en face," however, it appeared to be less dense, and therefore less clearly visible.

Discussion

Direct visualization of the fish bone foreign body in the cervical esophagus was obtained in 30 of the 40 proven cases (75%). This percentage compares most favorable with the demonstrability of chicken bone foreign bodies in similar location, although the latter are usually considered to be more easily visualized radiographically. (In a series of 55 cases of suspected chicken bone foreign bodies studied concomitantly, the bones were visualized in 34 instances (74%).)

Prevertebral space widening and collections of gas in these soft tissues have been stressed as important indirect signs of a foreign body. This study confirms the significance of these findings. The widening of the prevertebral space indicates edema and may appear early after lodging of the bone occurs. However, it was not associated with any complication except for one instance in the twelve cases of prevertebral widening. It is also of interest that our findings do not confirm Brown's (8) contention that prevertebral edema might tend to obscure a faintly visualized fish bone. On the other hand, the presence of gas bubbles in the prevertebral space is a sign of considerable gravity. All nine cases demonstrating this finding showed serious clinical complications.

Numerous investigators have advised the administration of contrast materials (bismuth, lipiodol, barium) to opacify the pharyngoesophageal regions so that foreign bodies not directly seen might become demonstrable, thus increasing the value of the radiographic examination. Opaque capsules, barium-soaked bread, and barium-soaked cotton have not proved to be of any noteworthy assistance in this author's experience. If barium is to be employed, the method which I have found most useful involves fluoroscopy of a barium swallow with "spot" filming followed by the water washout technique of Carlsund as described above. The objection to the use of barium—that it would coat the foreign body and make esophagoscopic identification more difficult—does not appear valid. As shown by roentgenographic studies, all of the barium emulsion is washed away from a normal mucosa upon drinking approximately eight ounces of water.

Knowledge of the expected densities of the various bones may be of considerable aid in interpreting the radiographic picture in cases of suspected fish bone foreign bodies. The investigation of radiopacity of the various fish bones found in the northeastern United States was greatly facilitated by the cervical phantom. Because of the marked radiographic similarity of the phantom to the human neck, the roentgenologic information obtained from the phantom studies should be applicable to clinical use. Thus, the type of fish eaten should be part of the history obtained by the roentgenologist. If a bone expected to be nonopaque were ingested, one could not expect its direct demonstrability on the film. Indirect evidence of its presence would be sought and barium employed, On the other hand, if the fish bone were of the radiopaque variety and no bone seen on the x-ray examination, this negative finding should be considered as significant. In the absence of distinct prevertebral swelling and gas collection it would appear safe simply to observe the patient without esophagoscopy. However, it should be noted that when severe symptoms persist, esophagoscopy may be required despite nonvisualization of fish bones deemed to be radiopaque. One explanation is that the bones may be situated in the thoracic esophagus and not easily visualized.

Flat bones appear much denser when seen "on end" than when radiographed "en face." Fortunately, most flat foreign bodies in the cervical esophagus lie in the coronal plane so that the lateral radiograph of the neck will visualize them "on end" (Fig. 6). This is well shown in the case of a haddock bone foreign body (Fig. 1). Occasionally, the flat bones may not lie in the exact coronal plane. For this reason, it may be desirable to radiograph the patient in slightly oblique positions if the suspected fish bone is not visualized in the lateral view.

The importance of technique merits emphasis. The roentgenograph should be taken with the finest focal spot available, a small cone, the shortest exposure time possible with the equipment (no longer than 1/20 second), and with some over exposure technique so that the resulting negative is slightly dark.

Of considerable interest is the observation that the bone was found at the level of the cricopharyngeus muscle in 17 cases and below the level of the cricopharyngeus but above the thoracic inlet in 22 cases. This suggests that the pharyngoesophageal sphincter is not only the cricopharyngeus muscle, but rather includes constrictor fibers in the upper end of the esophagus as well. Because the bone may lie low in the neck below the cricopharyngeus, it may be obscured by the clavicle and thicker parts of the thoracic inlet. If a radiograph is obtained while the patient enunciates the letter "E" or is in the act of swallowing, the bone lodged in the esophageal mucosa may ascend as the cricoid cartilage and attached esophagus rise during these acts. Such concealed bones may thus become visible just above the clavicle (Fig. 7).

The expected clinical densities of the various fish bones, as determined by the present phantom studies, are listed in Table V. It is possible that the given fish bone may vary from one group to

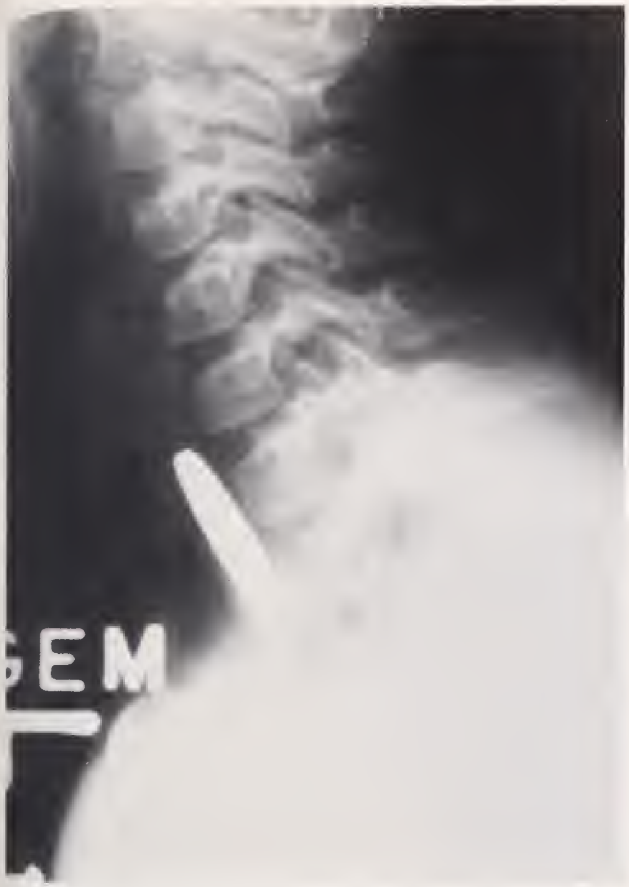

FIG. 6A. Coin foreign body in cervical esophagus lying in coronal plane. Seen "on end" in lateral view.

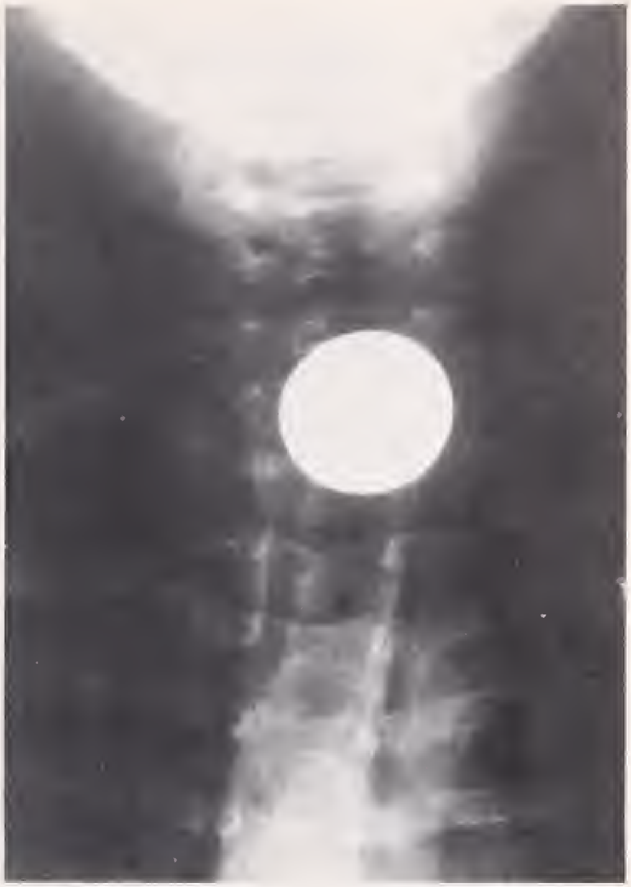

FIG. 6B. Same coin seen "en face" in frontal view.

the immediately adjacent group, but not to any greater extent. Thus, bones in Group I would not be expected to be entirely visible, or bones in Group III be very dense.

Conclusions

In 56 cases, the patient's symptoms appeared after the ingestion of the fish that suggested lodging of a fish bone foreign body. Such a bone was removed in 40 of these cases. The bone was directly visualized radiographically in 30 instances (75%).

Indirect evidence of the presence of a fish bone foreign body was characterized by prevertebral soft tissues swelling (21 cases) and gas collections in the prevertebral area (nine cases). The former indicated local edema and could appear quickly. The latter indicated a complication in all instances.

Opacification of the esophagus as an aid in the identification and localization of nonopaque fish bones is of value.

The radiopacity of bones from 21 species of fish commonly eaten along the eastern seaboard was investigated. The bones were suspended in water in a cervical phantom closely approximating the size, shape, and density of the human neck. It was found that radiographic technical factors influence the demonstrability of the various fish bones. A slightly over-exposed film best demon-

TABLE V

Expected Radiographic Density of Fish Bones

Group I Excellent Density	Group II Moderate to Slight Density
Bass	Bluefish
Codfish	Fresh Salmon
Flounder	Smoked Salmon
Fluke	Yellow Pike
Gray Sole	
Haddock	Group III Slight to no Radiopacity
Halibut	Butterfish
Porgie	Mackerel
Red Snapper	Pompano
Sea Bass	Trout
Smelt	
Striped Bass	
White Perch	

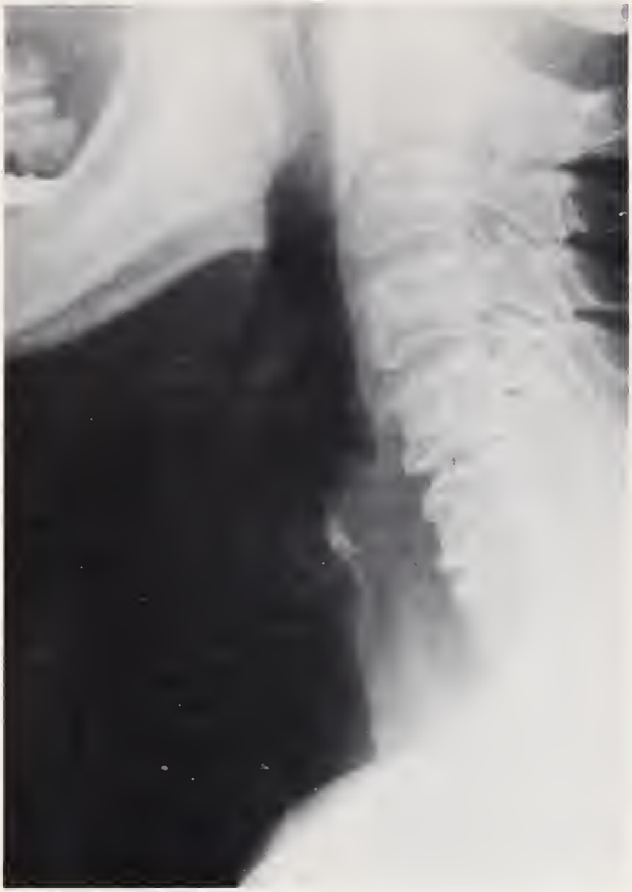

FIG. 7A. Fish bone foreign body at thoracic inlet, lower end not seen. Slight prevertebral soft tissue swelling present.

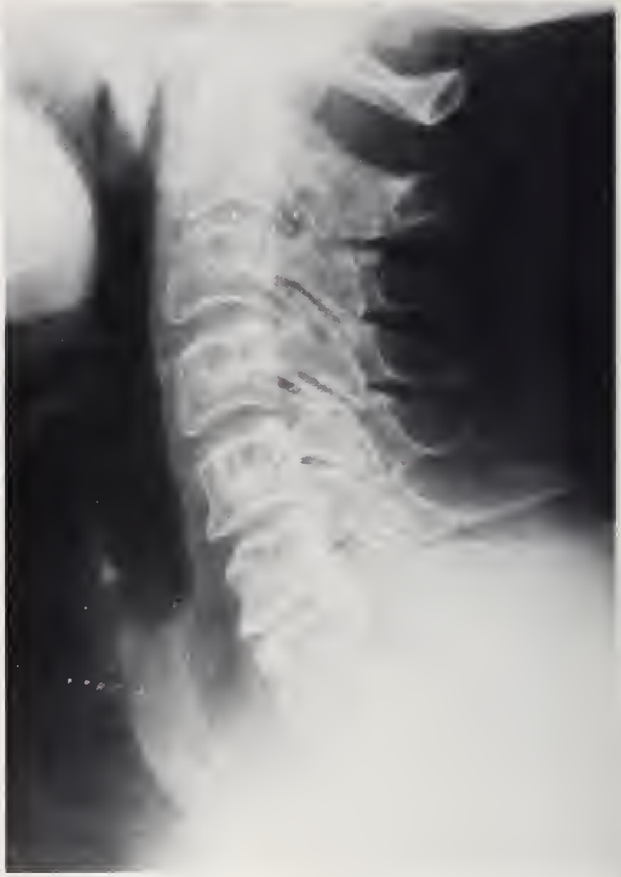

FIG. 7B. Film made with patient phonating letter "E". Notice rise of bone above thoracic inlet so that lower end is now visible.

strates their presence. Cooking of the fish does not alter the radiopacity of their bones. Finally, a table listing the radiopacities of the various fish bones studied is presented. This knowledge is considered to have predictive and clinical significance. It is suggested that similar data on fish bones in other regions be acquired.

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Trabecular Patterns and the Internal Architecture of Bone

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Twenty years ago when we began our early investigations on roentgen changes in bone in response to trauma, avascularity, and during repair, we confronted Dr. Bernard Wolf with a number of confusing findings and asked for his help. After studying the material, he responded with his usual twinkle, "If you x-ray a large bottle of aspirin tablets I think you will find the answer." I anticipated an image of a bottle outlining a uniformly grey shadow, but instead there appeared to be a single layer of tablets (Fig. 1a) Dr. Wolf's response to my surprise was, "Of course—it's summation." Indeed, this keen observation, so typical of Dr. Wolf's brilliance and complete grasp of fundamental principles opened the door to an investigative protocol that led to our better understanding of dynamics of the skeletal system (33).

A roentgenographic examination of bone is a single plane black and white image of accumulated densities and lucencies that does not represent an exact picture of the anatomy of the part itself. In practice, we integrate our clinical experiences and knowledge of diseases with these photographic patterns, equating normal and abnormal with recognizable alterations. Trabecular patterns of individual bones vary depending upon the density and relationship of fine and coarse trabeculae and are influenced by biomechanical forces (34, 41) and changes in the body's internal physiologic milieu (6, 8, 13, 15, 21, 39). In bone, fracture healing, tumors, inflammatory, metabolic and degenerative diseases are recognized by gross changes in density and lucency.

The roentgen anatomy of cancellous bone is essentially that of the interrelationship of fine and coarse trabeculae (19, 20, 28, 30, 35, 41). Coarse trabeculae are generally oriented along the lines of stress of a long bone, being more prominent at both compression and tension sites. Change in the direction of forces as a result of realignment following fracture or surgery will result in absorption of the existing coarse trabeculae and their redevelopment along new lines of stress. Fine trabeculae may exist either as cross-bracing struts between the coarse major weight bearing trabeculae or relatively homogeneously tightly packed at sites subjected to constant changing dynamic forces as at subchondral joint surfaces. In the economy of effort, areas in which little or no force is applied, as in Ward's triangle in the neck of the femur or in the os calcis at the angle between the diverging coarse trabecular weight bearing axes, fine trabeculae are sparce or nonexistent. This discussion will review several fundamental principles regarding the characteristics of trabecular structure and the nature of alterations that occur based on clinical and experimental observations.

Thin sections of a bone reveal that the structural relationships of fine to coarse trabeculae are different in each, and that none appears exactly the same as a roentgenogram of the bone as a whole. The phenomenon of summation (30) represents a pattern that clinicians recognize as a normal image although it is not a true anatomic representation of any individual segment. Alterations in a roentgen pattern have been identified clinically with physiologic changes in bone in specific diseases, but the relationships of roentgen patterns and the mechanism of summation have not been clarified.

Types of Summation

In bone, two summation types can be identified, namely a pattern similar to the individual superimposed structures themselves, or one that is different.

Similar Pattern. When x-rayed in the mass, a group of homogeneous forms may summate to reproduce the image of a single form. Changes in positioning or randomization of the mass may

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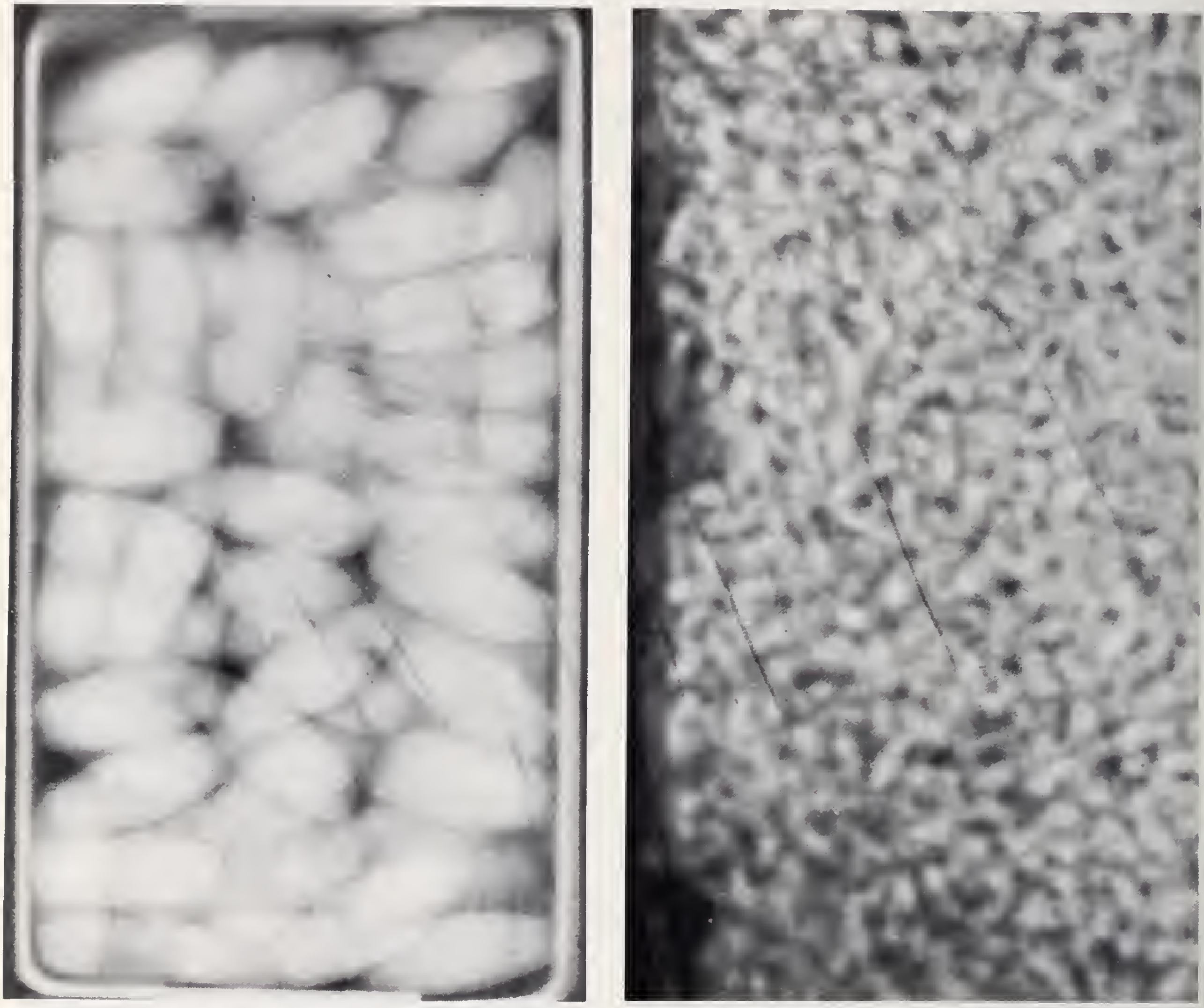

FIG. 1. Summation to a similar pattern. a) X-ray of a bottle of aspirin tablets summated to a thin layer of identifiable tablets. b) X-ray of a large box of rice summated to a single layer of rice granules.

alter the pattern, but each summated roentgenogram will be that of a single form or layer of that form. *Examples are:* X-ray of a large bottle of aspirin tablets (Fig. 1a) or of a box of thousands of grains of rice (Fig. 1b) will appear as though there were a single layer of aspirin or rice respectively.

Clinically, in osteochondromatosis (Fig. 2) in which a joint may be packed with many overlapping loose bodies, a pattern of a layer of a smaller number of bodies will appear on the x-ray. In bone, large numbers of small metastatic overlapping areas may be recognizable as individual or small groups of lytic or blastic shadows.

Different Pattern. A summated roentgenographic pattern may not reflect the anatomy of the individual components. For example, one screen added to another in a random fashion will produce a stellate pattern when three screens are superimposed (Fig. 3a). A larger number of screens will exhibit a similar pattern suggesting the phenomenon of summation of trabeculae in bone (Fig. 3b). Similarly, multiple microscopic lytic or blastic areas (lung, bone), which may not be obvious grossly on dissection, may summate into a miliary pattern.

Since the roentgenogram frequently identifies an abnormality by its pattern rather than its precise anatomy, the surgeon must be prepared to deal with a circumstance which may be different from the x-ray itself. For example, he should not be satisfied when he has removed the number of loose bodies he has counted on the roentgenogram in osteochondromatosis but should search all recesses for additional bodies that may have been camouflaged by summation. Nor does a normal

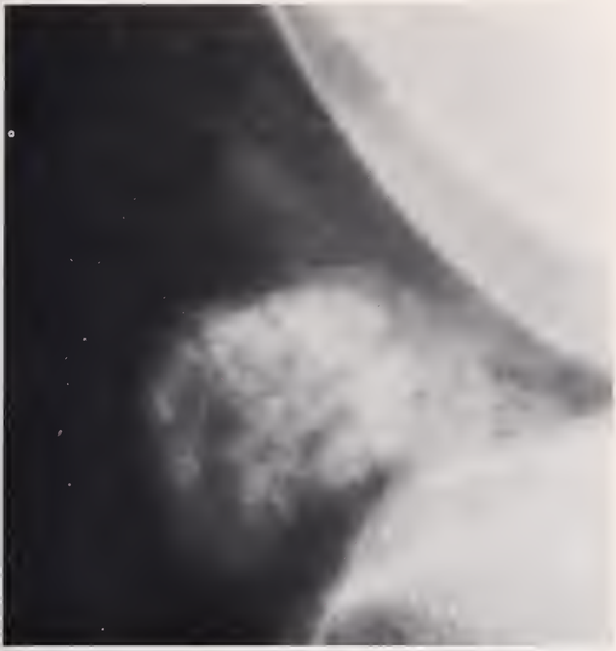

FIG. 2. X-ray of a knee in a patient with osteochondromatosis demonstrating an identifiable number of loose bodies. At surgery, many more osteochondral bodies were found than identified roentgenographically preoperatively.

roentgenogram rule out bone destruction since a large number of summated units must be removed or destroyed (up to 50% of the bone itself) before the trabecular pattern is affected.

Dynamics of Bone Atrophy and Its Clinical Significance

Maintenance of normal trabecular and cancellous integrity in bone depends upon a healthy balance between the internal and external milieu. Many clinical conditions can be identified as being associated with varying degrees of bone atrophy. These include idiopathic osteoporosis, nutritional lack or failure of absorption of mineral and protein requirements, disturbance of osteogenic (calcitonin) and osteolytic (hyperparathyroid, thyroid, adrenal) balance, hyperemia resulting from inflammation (rheumatoid arthritis), infection or increased vascularity (A-V fistula).

Biomechanical influences play a major role. Weightlessness caused by periods of high altitude existence, atrophy of disuse following fracture

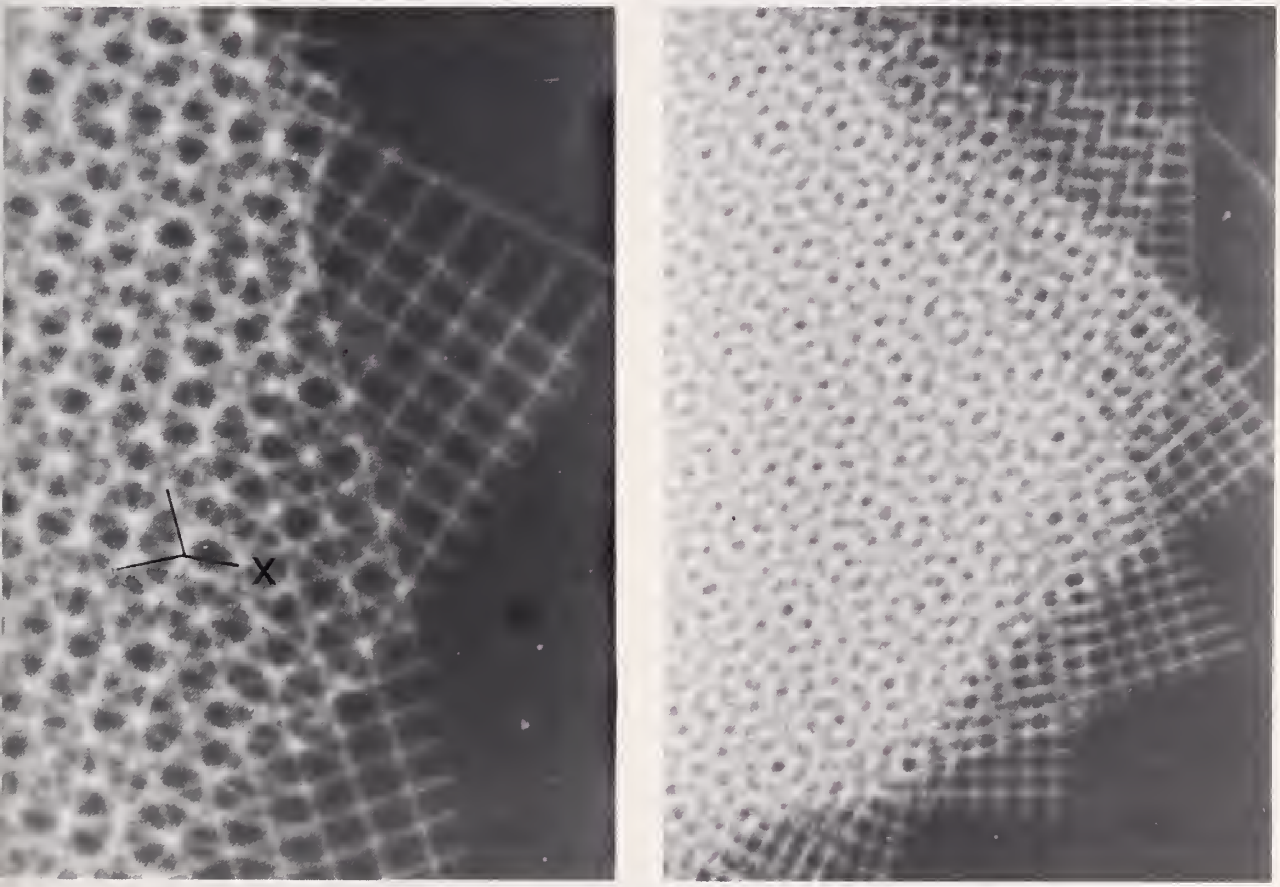

FIG. 3. a) Three randomly overlapped screens. Two overlapping screens can be identified individually but these screens produce a "rosette" pattern (x) which b) persists as more and more screens are added (here 10 screens).

immobilization or decreased muscle tone resulting from primary muscle or tendon tears are examples. Recent laboratory and clinical experiments have suggested that osteoblast and osteoclast activity associated with bone formation and absorption respectively appear to be the result of biomechanically induced positive and negative electrical charges in bone. Regardless of the etiology, the roentgenographic appearance of bone atrophy is characteristic. It may be recorded grossly by measurements of bone density (4, 9, 11, 18, 23, 27, 38) using densitometry, or visually by comparison with standards. One may suspect 30 percent demineralization of bone, but 50 percent is generally necessary to be unequivocal (3). Localized lesions may be recognized by differences in density compared with the unaffected segment, a round lesion being more difficult to identify than one with a sharp border in which the density gradient is abrupt rather than gradual. In addition, bone is not completely homogeneous and responds differently to the same insult in different areas, partially dependent upon the vascular anatomy. Quantitative observations may at times be of limited value but studies of trabecular alterations may permit the physician to identify early and qualitative alterations, facilitate early evaluations of success or failure of intervention, and follow sequential changes of disease that affect bone.

Knowledge of sequential roentgenograms of a bone during the process of atrophy as compared with that of the normal opposite side, and a knowledge of the normal patterns of a particular bone at a specific age are essential in appreciating the importance of trabecular architecture in clinical medicine. Bone atrophy, regardless of its etiology, is a surface phenomenon of endosteal tissues that are induced to become osteoclastic (Fig. 4). Except in osteomalacia in which uncalcified bone matrix may form, loss of bone substance during atrophy or normal physiologic turnover is characterized by loss of both matrix and minerals. All trabecular surfaces are affected simultaneously, the sequential changes therefore being an expression of the anatomic width of each trabeculum and the architectural structure of that segment of bone. For example, in areas of concentrated stress as in the femoral condyles, there are heavy longitudinal coarse trajectory trabeculae and fine lace-like bracing trabeculae. On the roentgenogram, the prominence of the trajectory trabeculae is partly camouflaged by the overlay of the large number of fine trabeculae. Surface osteoclasis during the process of atrophy results in thinning and disappearance of the fine trabeculae (1, 33). In the absence of the fine trabecular veil, the coarse trabeculae, which themselves are thinned to some degree, appear more prominent. This trabecular coarsening which can be demonstrated experimentally (33) is one of the first signs of bone atrophy.

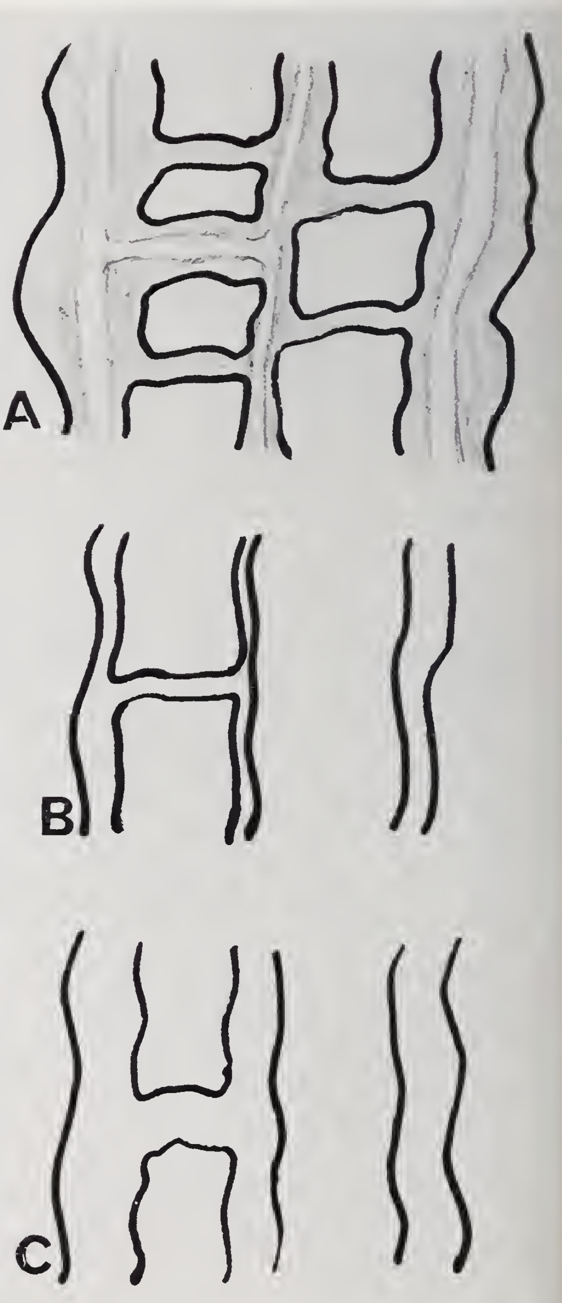

Fig. 4. Diagrammatic sequence of bone atrophy and repair a) A normal bone may be subjected to uniform surface osteoclasis and absorption (shaded) leading to b) loss of fine trabeculae and thinning of longitudinal trajectory trabeculae that stand out more prominently when fine have been absorbed. c) Reconstitution occurs as new bone forms on the scaffold of the remaining trajectory trabeculae with less reformation of the fine trabeculae resulting in a coarsened roentgen pattern.

In areas in which only fine trabeculae exist (subchondral articular surfaces, head of the femur, condyles of the metatarsals, etc.), uniform loss of bone mass up to 50 percent does not affect the summation trabecular pattern and may not be recognizable roentgenographically. Further atrophy may result in discontinuity of sufficient numbers of trabeculae to alter the characteristic pattern itself. Within completely cancellous structures, early signs of atrophy and bone absorption may be detected in regions that have greater vascularity, notably immediately below the articular subchondral bone plate and at the site of the old longitudinal growth plate. An x-ray beam that is tangential to dome shaped subchondral bone traverses fewer trabeculae, permitting early detection of loss or change in pattern. Atrophy may be spotty rather than uniform, producing a summated pattern of trabecular irregularity or isolated lytic areas.

When the process of atrophy ceases, bone repair begins. Endosteal osteogenesis results in the deposit of new bone on the remaining trabeculae as a scaffold, much like the incorporation of bone grafts. There is little tendency for reformation of former fine cross bracing trabeculae that had been absorbed. As demonstrated experimentally, the remaining heavy major supporting trajectory trabeculae become thicker resulting in an increase in coarsening of the pattern until such time as adequate bone strength has been attained for biomechanical needs (33). Except for relatively minor remodelling, over the years this pattern has remained as a longstanding record of a former episode of atrophy (Fig. 5).

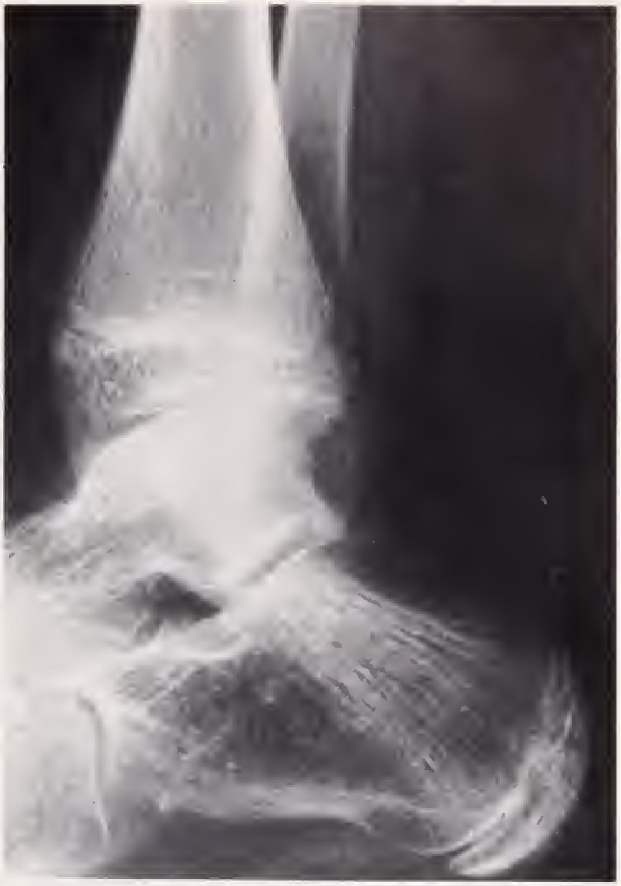

FIG. 5. X-ray of the ankle of a patient immobilized for three months in a long leg plaster cast for a fracture of the tibia six months after return to normal activity. The longitudinal trabeculae have thickened with little reformation of the fine trabeculae, leaving permanent coarsening of the roentgen pattern.

In addition to assessing sequential changes in bone during states of localized or generalized idiopathic or specific atrophy and repair, the general principles of the behavior of trabecular patterns are helpful in diagnosis and followup, most notably in avascular necrosis and incorporation of bone transplants.

Avascular Necrosis

The x-ray diagnosis of avascular necrosis is generally based on localized increase in density. It had been argued for a long time that dead bone absorbed local calcium salts making it stand out against the background of less dense bone rendered osteoporotic by disuse and local increase in vascularity induced by the reparative process. Phemister (24) observed that necrotic bone retains its original architecture because of its failure to take part in surrounding bone atrophy (6, 22, 25, 40), and Babechko and Harris (6) explained increased graft density as invading new bone forming on the necrotic trabeculae. Further information regarding the relationship between viability of bone and its vascularity is being accumulated using radioisotope scanning. Lack of uniformity in the degree of involvement and in the mechanism of repair, the variation in vascular patterns, and poor information regarding clinical significance relative to symptoms and function make gross information of this nature of limited value.

In orthopaedics, avascular necrosis of the head of the femur following intracapsular fracture or traumatic dislocation presents a major problem. Replacement of the femoral head and joint replacement in the elderly at the time of injury have been employed to avoid this complication. In the younger adult however, the value of a healed fracture is superior to a prosthesis, and internal fixation is generally the treatment of choice. There is an incidence however, of 40–60 percent of avascular necrosis requiring later reconstructive surgery. Early detection of a viable head permits early rehabilitation, and early diagnosis of bone necrosis can avoid long periods of disability and morbidity before the decision is made to perform a reconstructive procedure. The signs of bone atrophy noted above, namely trabecular thinning, discontinuity, and absorption, are first apparent in the subchondral area of a femoral head or at the head-neck junction, superiorly and inferiorly where fine trabeculae are normally sparse. These findings may appear as early as the first two or three months, and frequently as early as six weeks following injury indicating that vascularity to the head of the femur was not disturbed (Fig. 6a). Later, these same findings of atrophy in the subchondral area are suggestive of avascular necrosis as invading new blood vessels penetrate the necrotic femoral head. Timing, therefore, is important in evaluating changes in a bone roentgen.

Prospective planning to use these diagnostic signs demands that all x-rays from the time of injury and surgery be taken in the same position with the same exposure to permit assessment of the trabecular changes occurring within the femoral head and relative atrophy of the head and surrounding bone of the trochanter, proximal femur, and acetabulum. The posterior acetabular shadow which normally overlays the head may be confusing, but x-rays in abduction and adduction as well as in lateral projection are helpful. It is frequently possible to differentiate the trabeculae within the head and acetabulum because of their different internal architectures. Similarly, avascular necrosis of the carpal navicular and the body of the talus can be detected by these criteria (Fig. 6b). Since the rate of bone atrophy varies greatly in different locations, absence of characteristic changes should not necessarily be considered as an early sign of bone necrosis. With time,

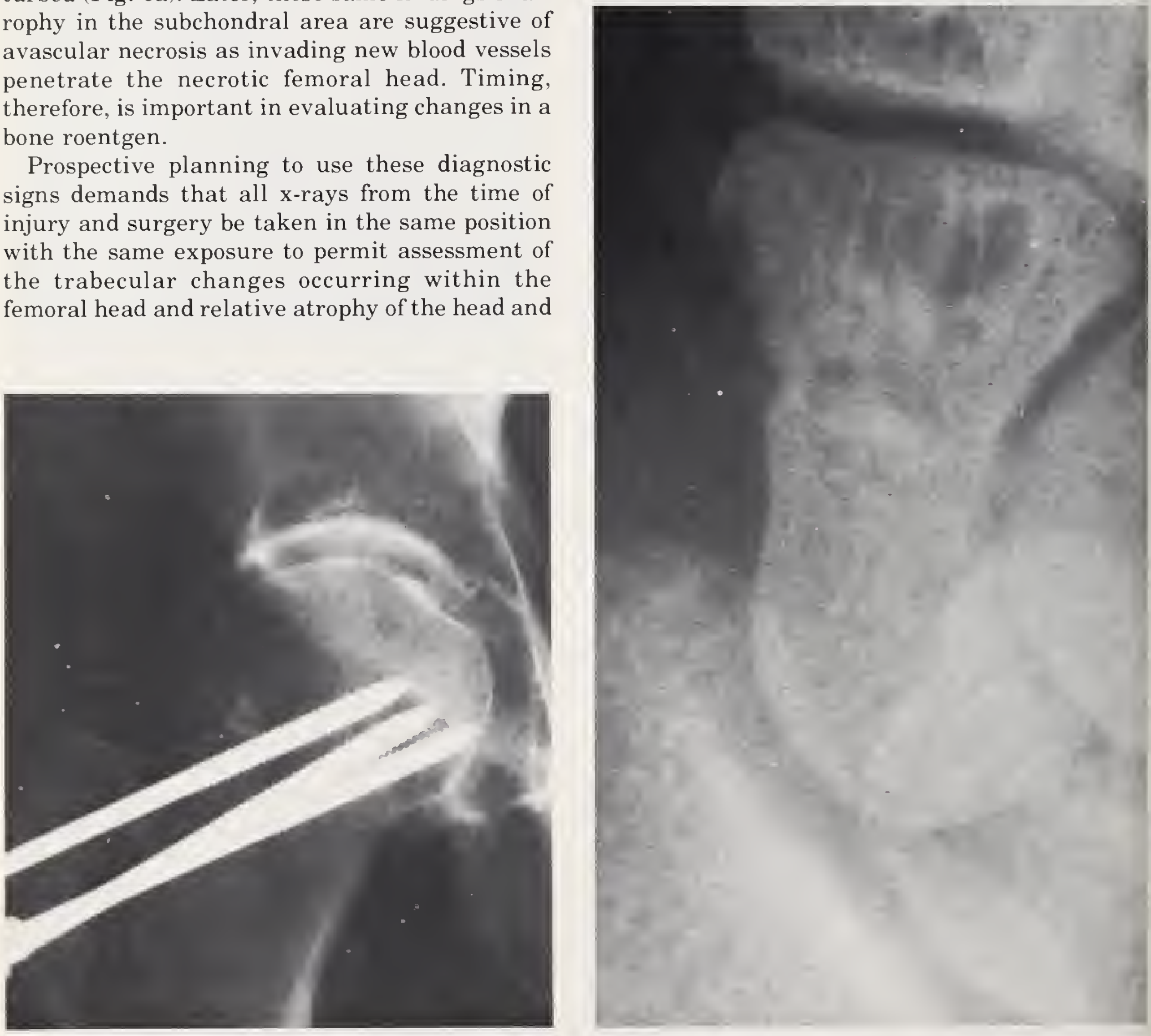

FIG. 6. a) X-ray of the femoral head in a 62-year-old female six weeks following intracapsular fracture and internal fixation. Viability of the head can be determined by the presence of bone atrophy as evidenced by loss of continuity and absorption of fine trabeculae. b) Avascular necrosis of the proximal fragment of a fractured carpal navicular is evidenced by maintenance of the fine trabeculae in the presence of atrophy and coarsening within the distal viable fragment.

the longer the original pattern persists the greater the suspicion of osteonecrosis.

Bone Transplants

For the most part, transplanted cancellous bone becomes necrotic. Although some endosteal cells may remain viable, it is unlikely that they contribute significantly to the success of the graft (32). A necrotic unincorporating transplant may present a dense appearance on the roentgenogram (26). Essentially, graft survives as a scaffold for invasion by host bone. The process of incorporation appears to represent a balance between osteolytic influences of inflammatory granulation tissue and the host potential to elaborate a reparative osteogenic response. Because of size, overlap and positioning, it is not practical to apply density measurements to graft incorporation and assessment of internal architectural changes may be of clinical value.

Bone transplants may exhibit characteristic trabecular architectural changes:

Osteolysis

In the presence of poor host osteogenic potential, or unfavorable local circumstances including large hematoma, poor circulation, motion or a gap between graft and host bone, intertrabecular spaces of a transplant are invaded by granulation tissue. Osteoclasis, as occurs in bone atrophy is noted at all graft surfaces. Mottling of the graft, absorption and discontinuity of trabeculae and the appearance of fragmentation are noted on the x-ray (Fig. 7). Osteolysis is common when very small grafts are used and not packed densely and closely against the host bone. It should be noted that atrophy associated with healthy vascularity is a good sign when avascular necrosis is suspected following injury, but signifies osteoclasis in bone transplants.

Incorporation

Increased density of a bone graft is generally an indication of new bone formation. The osteogenic front arising from the host enters the graft and creeps along scaffolding of necrotic trabeculae. When the intertrabecular spaces are filled with new bone, the graft takes on a ground glass appearance and the summated fine trabecular pattern disappears (Fig. 8). Medium sized grafts of cancellous bone fixed firmly to the host surface, and preservation of periosteal vascularity generally favor rapid incorporation.

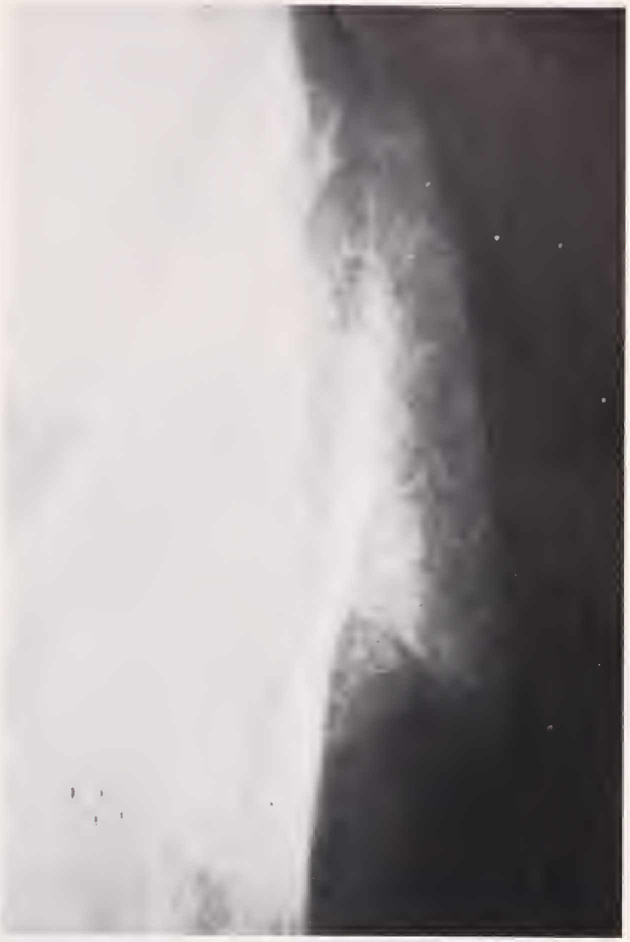

FIG. 7. Absorption and failure of incorporation of a bone graft may be evidenced by areas of mottling and absorption as a result of osteoclastic granulating tissue invasion.

Varying combinations of these architectural changes may be noted. A preliminary period of bone atrophy may precede a vigorous osteogenic response and bone atrophy may be noted before incorporation. A graft that retains its appearance unchanged from its original state as it is surrounded by fibroplastic response is generally one that eventually becomes atrophic and is absorbed rather than incorporated.

Conclusion

Alterations in the structure of bone in response to biomechanical forces or changes in the body's internal milieu are best reflected in the trabecular structure. Recognition of these changes in addition to gross impressions and measurements of alterations and density are helpful in early diagnosis and in following sequential changes during disease or reparative periods. The summated patterns in bone vary depending upon the density

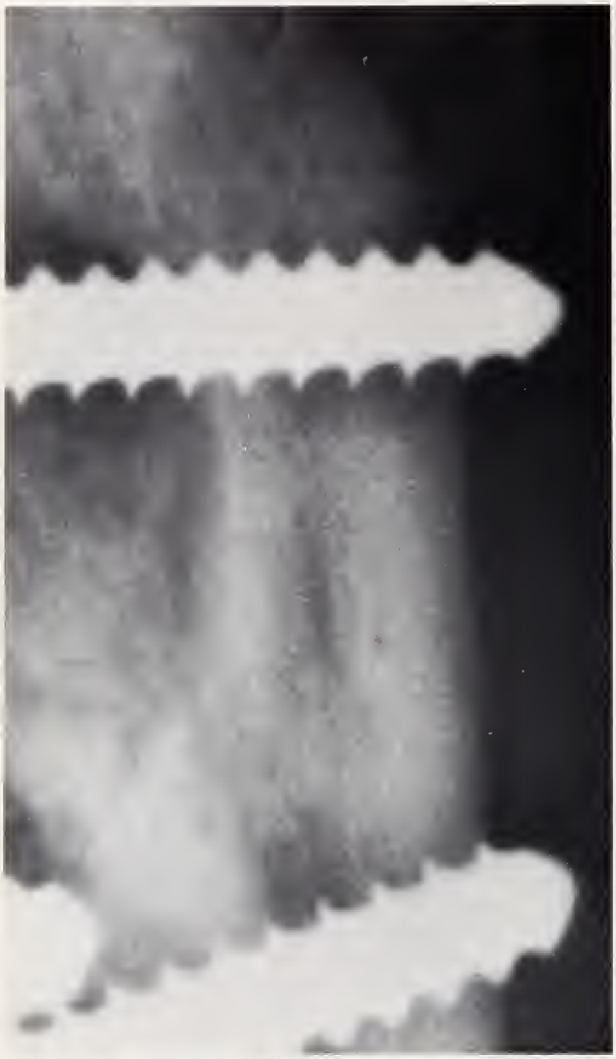

FIG. 8. Incorporation of a bone graft occurs as a result of new bone growing along transplanted trabeculae and filling intertrabecular spaces. These changes are reflected in increased homogeneous density on the roentgenogram.

and relationship of fine and coarse trabeculae which vary at different anatomic locations.

Bone atrophy, which may be the result of alterations in the body's physiologic state, hyperemia, disuse, or inflammation results in surface osteoclasis. Very fine trabeculae are absorbed and medium sized and coarse trabeculae thinned. During repair, new bone forms on the scaffold of the remaining trabeculae producing a different pattern that remains as a permanent document of the episode. Absence of physiologic response due to lack of vascularity can be recognized by failure of that segment of bone to become atrophic. Viability of an injured bone, most notably in fracture of the neck of the femur, carpal scaphoid and talus, can be detected by absorption of fine trabeculae and is the earliest assurance that avascular necrosis has not occurred. Late findings of subchondral atrophy however, are associated with early vascular invasion of necrotic bone. Similar findings are noted during bone graft incorporation, but their significance is different, namely, absorption of fine trabeculae signifies osteoclasis and invasion by nonosteogenic granulation tissue eventually leading to bone graft absorption, while a ground glass appearance is associated with incorporation as new bone fills the intertrabecular spaces.

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When to Question the Diagnosis of Anaplastic Carcinoma

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Rarely can a radiologist make a specific diagnosis in paranasal sinus tumors. It usually is the role of the pathologist to establish a specific histology. There are, however, instances when this histologic diagnosis does not coincide with the roentgen appearance. When this occurs the radiologist must question the diagnosis and the clinician should consider a rebiopsy for electron microscopy and/or histochemical testing.

This set of circumstances is especially likely to happen when the histologic diagnosis is given as anaplastic carcinoma. Specifically, there is a small group of tumors that histologically can be confused with anaplastic carcinoma and it is the differentiation of these lesions that is the focus of this paper. In addition, the coexistence of a mucocele and anaplastic carcinoma can present a confusing radiographic picture and erroneously suggest an alternate diagnosis.

We present the roentgen findings that should alert the radiologist to question the diagnosis of anaplastic carcinoma and to review the several tumors that must be considered in the differential diagnosis.

Squamous cell carcinomas are the most common malignancies affecting the nasal cavity and paranasal sinuses. They account for between 80%–90% of all the tumors (1). These epithelial tumors have a varied histology ranging from well differentiated keratinizing lesions to poorly differentiated nonkeratinizing and/or anaplastic carcinomas. It is the lack of cellular differentiation in the anaplastic group that allows histologic confusing with other poorly differentiated tumors. Specifically, these tumors include esthesioneuroblastomas, histiocytic lymphomas, embryonal rhabdomyosarcomas, melanomas and plasmacytomas (2). As a group, all these nonepithelial lesions represent less than ten percent of all sinonasal malignancies and as such require a high clinical index of suspicion to justify their being offered as a primary diagnosis.

One of the clinical problems in sinonasal cavity malignancies is the relatively advanced state of tumor destruction that has occurred prior to the patient's presenting for initial clinical evaluation. The explanation of this phenomenon probably lies in the unexplained lack of pain associated with both soft tissue and bony destruction. It is usually a secondary symptom such as nasal obstruction, epistaxis, proptosis or facial deformity that brings the patient to the initial presentation. Pain is almost always indicative of an associated infection whether clinical or subclinical in nature.

As such, the initial roentgen examination is usually of a fairly sizable soft tissue mass with various degrees of associated bone destruction. It is the overall pattern of the tumor mass and the bone destruction that either suggests a diagnosis of anaplastic carcinoma or an alternate possibility.

Squamous cell carcinomas radiographically always present as soft tissue masses and there is associated adjacent bone destruction in 70%–80% of the cases (Fig. 1). This bone destruction is permeative and aggressive in nature and occurs rapidly enough to destroy the bone before it can be pushed outwards by the tumor mass (Figs. 2, 3). Thus, expansion of the sinonasal cavity around a tumor mass is unlikely to be caused by anaplastic carcinoma alone (3).

The coexistence of a mucocele with an anaplastic carcinoma does occur and would explain the roentgen findings of expansion in the presence of a definite carcinoma histology. With expansion, the radiologist should either invoke the coexistence of a mucocele or suggest an alternate diagnosis.

Secondly, it is unusual for an anaplastic carcinoma not to involve most of the bone adjacent to its margins. Although sizable anaplastic tumor masses may not destroy the peripheral bone, the vast majority of such tumors do. A sizable tumor

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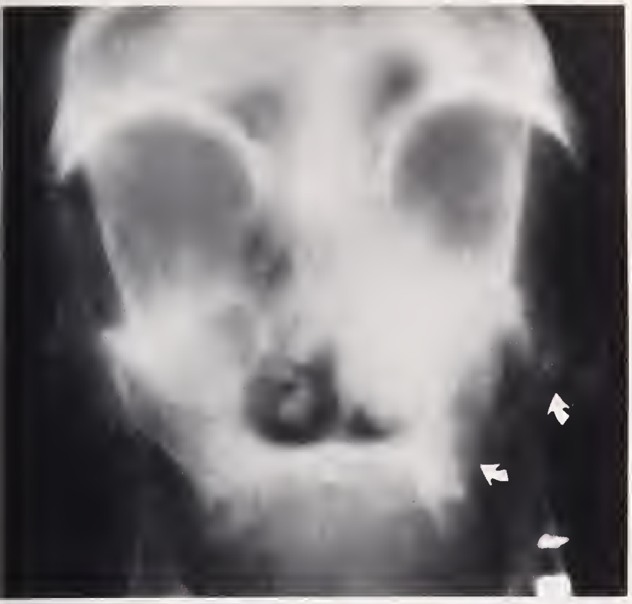

FIG. 1. Coronal tomogram reveals a soft tissue mass in both ethmoids, the right antrum and nasal cavity. There is bone destruction of the right orbital floor and medial wall as well as the lateral antral wall and zygoma (arrows). Inflammatory disease was present in the left antrum. Squamous cell carcinoma.

mass with most of the peripheral bony margins intact would be an unusual presentation for anaplastic carcinoma and should at least raise the question of an alternate diagnosis.

In the select group of tumors mentioned as being possibly confused at the light microscopic level, histiocytic lymphoma, esthesioneuroblastoma and, to a lesser degree, plasmacytoma usually present a roentgen picture of slight expansion of the surrounding sinonasal bony margins with most of the peripheral margins intact (Figs. 4–8). Melanomas and embryonal rhabdomyosarcomas can present pictures either of expansion or aggressive destruction as seen in anaplastic carcinoma (Figs. 9–12). Thus, the spe-

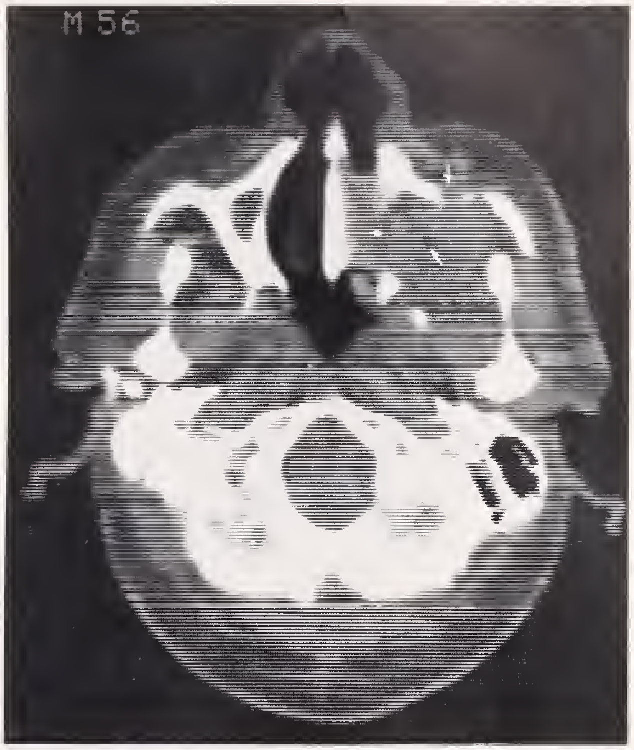

FIG. 3. Axial CT scan reveals a soft tissue mass in the left antrum and nasal cavity. Arrows indicate the extensive areas of bone destruction of the antral walls (compare to normal right side). Squamous cell carcinoma.

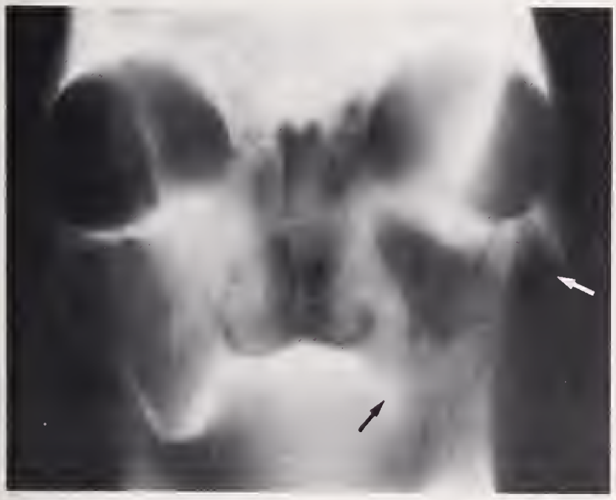

FIG. 2. Coronal tomogram reveals destruction of the left maxillary alveolus and lateral antral wall up to and including the zygoma (between arrows). The left orbital floor is also destroyed. Squamous cell carcinoma.

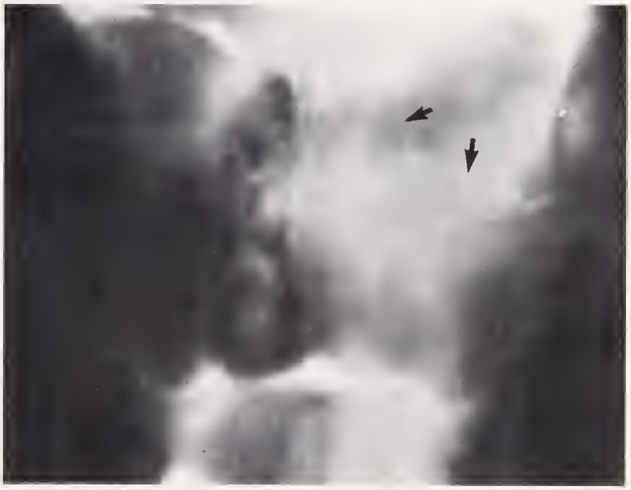

FIG. 4. Coronal tomogram on a patient with a biopsy of carcinoma reveals an expansile soft tissue mass of the left ethmoid, maxillary sinus and nasal cavity. The left orbital floor and medial wall are intact and pushed upwards. There was a small anaplastic carcinoma at the base of the left maxillary sinus and all the rest of the mass was a mucocele.

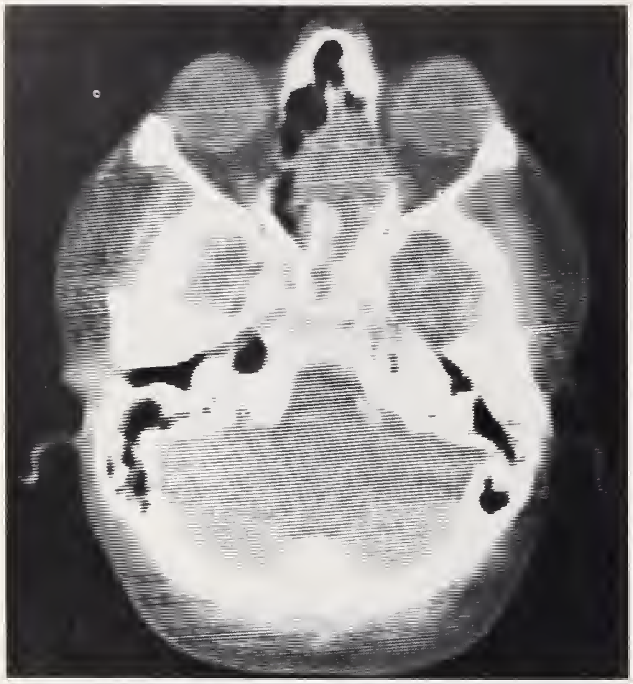

FIG. 5A. Axial CT scan on a patient with a biopsy of squamous cell carcinoma reveals an expansile ethmoid mass which extends into the sphenoid sinus. There is little bone destruction evident.

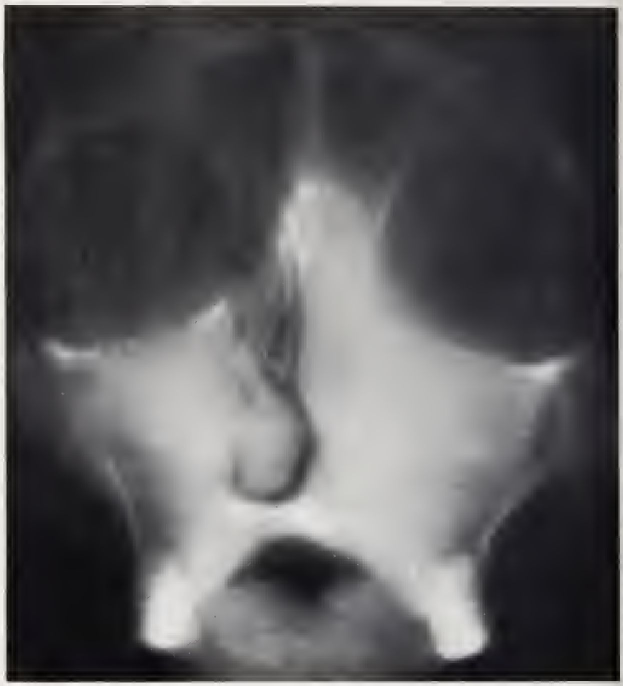

FIG. 6. Coronal tomogram reveals an extensive bilateral soft tissue mass of the left ethmoid and nasal cavity and both maxillary sinuses. Virtually all the outer bony margins are intact. Histiocytic lymphoma.

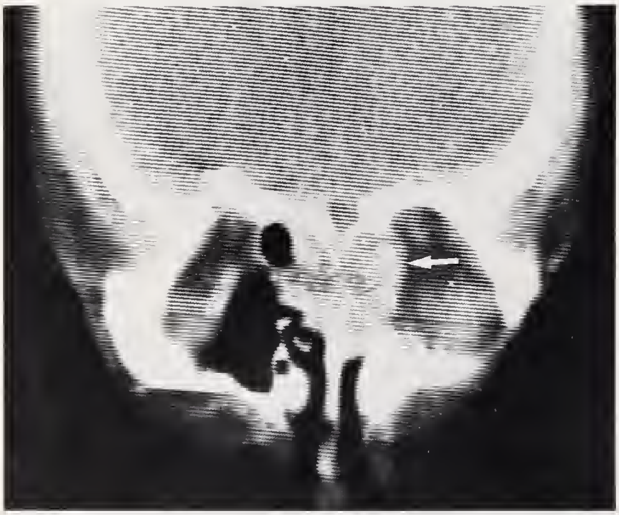

FIG. 5B. Coronal CT confirms the expansile nature of the mass with an intact lamina papyracea or medial orbital wall (arrow). Squamous cell carcinoma with an ethmoid mucocele.

cific diagnosis will depend upon the clinical presentation and ultimately the rebiopsy.

Signs and symptoms of sinonasal tumors are nonspecific and related more to the anatomy of this region than to a specific etiology. Nasal obstruction, rhinorrhea, and epistaxis are the most common symptoms and most of these noncarcinomatous lesions present clinically as polypoid masses. The clinical points that we have found most helpful are the age of the patient and the location of the lesion (Table I) (1, 4–6). Embryonal rhabdomyosarcomas and esthesioneuroblastomas tend to occur at younger ages and

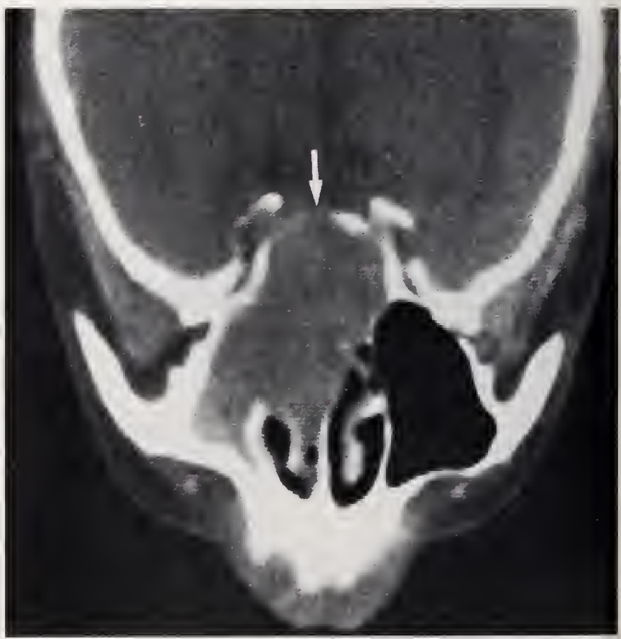

FIG. 7. Coronal CT scan reveals an expansile mass of the right maxillary sinus, nasal cavity and sphenoethmoid region. Only a focal area of destruction is seen (arrow), the remaining bony margins being intact. Plasmacytoma.

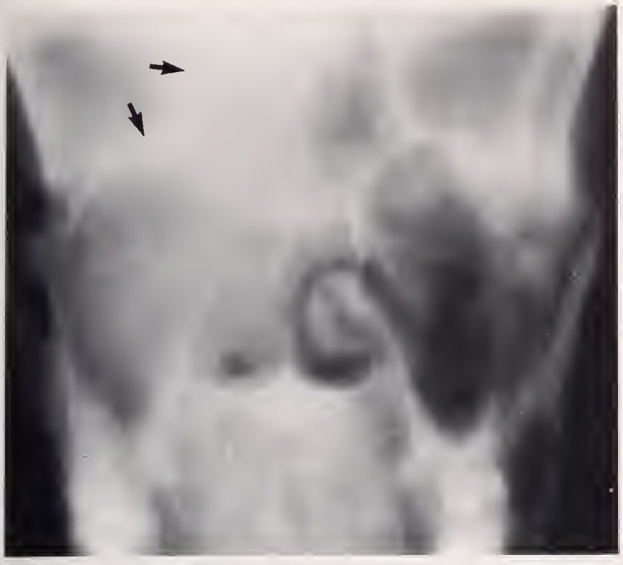

Fig. 8. Coronal CT scan on a patient with a biopsy of anaplastic carcinoma. There is a soft tissue mass in the right ethmoid and maxillary sinus and nasal cavity. The outer bony margins are intact and in particular the right medial orbital wall and floor (arrows) are not destroyed. There is also slight expansion of the entire region containing the mass. Esthesioneuroblastoma of the ethmoid sinus with a mucocele of the antrum.

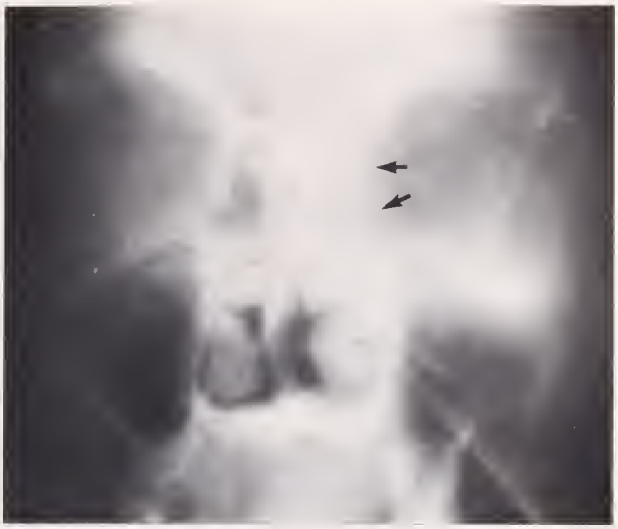

Fig. 10. Coronal tomogram reveals a left ethmoid soft tissue mass which extends into the upper left antrum. The medial orbital wall is intact (arrows). This would be an unusual presentation of squamous cell carcinoma. Embryonal Rhabdomyosarcoma.

esthesioneuroblastomas occur mainly in the upper third of the nasal cavity while melanomas tend to occupy the lower third of the nasal cavity.

Obviously, the pathologist is the only final means of establishing a definite diagnosis; however, because of the potential confusion at the light microscopic level, electron microscopy (EM) and special histoclinical stains must be utilized to ascertain the true cell of origin. Table II lists these tests and their findings (7, 8). In some cases, they will result in a change of the diagnosis from anaplastic carcinoma, while in other cases the carcinoma will be confirmed. In these cases, the

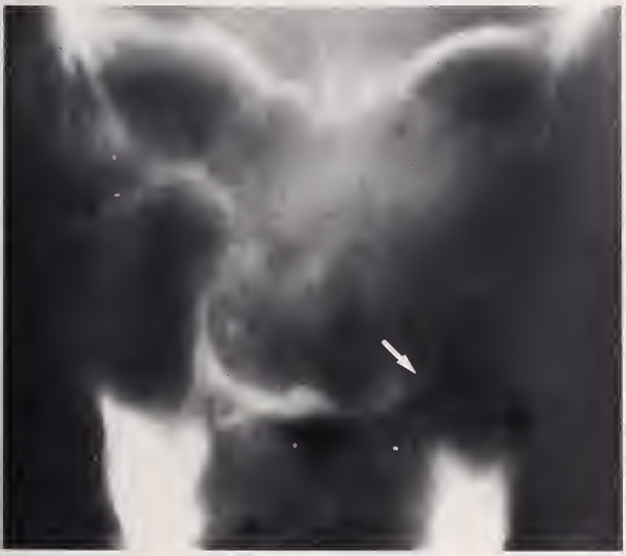

Fig. 9. Coronal tomogram reveals a large soft tissue mass in the nasal cavity, both ethmoid sinuses and left antrum. Areas of bone destruction are present on the left side while the right bony margin is intact. Some outward expansion of the lower left nasal vault is present (arrow). Embryonal Rhabdomyosarcoma.

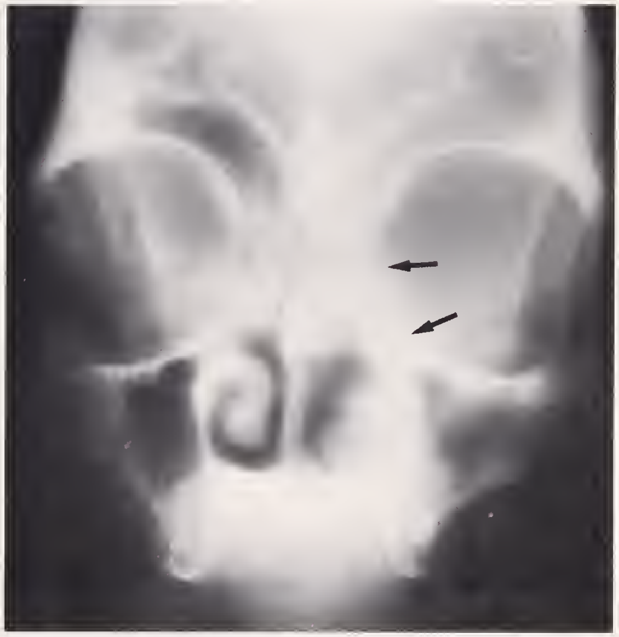

Fig. 11. Coronal tomogram reveals a soft tissue mass in the left ethmoid which extends downward into the nasal cavity and upwards into the supra-orbital region. The nasal septum is intact, however, there is destruction of the medial wall of the left orbit (arrows). Melenoma.

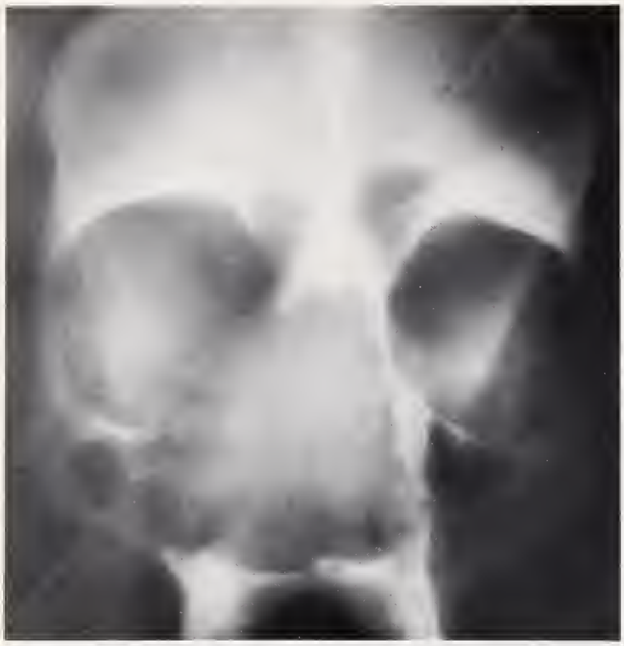

Fig. 12. Coronal tomogram reveals a large soft tissue mass in the nasal cavity, left antrum and both ethmoid sinuses. There is destruction of the right orbital floor and medial wall and the lateral wall of the nasal vault. This could be a squamous cell carcinoma, however, the slight degree of expansion would be unusual. Melenoma.

presence of expansions implies the coexistence of a mucocele.

The concerns about establishing a correct final diagnosis are not just academic curiosity since the treatment plan has to be modified according to the diagnosis. Specifically, if the diagnosis of anaplastic carcinoma is confirmed, preoperative irradiation may be indicated. However, if radiographic expansion is present the surgery should be performed prior to irradiation. This is especially true if the preoperative fields include the eye. Blindness may be needlessly caused because a field was set too large in order to encompass the unsuspected, associated mass of the mucocele. In addition, the mucoceles lack of response to irradiation and/or chemotherapy could erroneously be interpreted as a lack of tumor response.

Although combined radiation therapy and surgery are the present treatment of choice for esthesioneuroblastomas, plasmacytomas, and anaplastic carcinomas, they are not the primary treatment plan for all of the tumors in our differential diagnosis. Chemotherapy is added to the regimen for embryonal rhabdomyosarcomas while irradiation alone is suggested for histiocytic lymphoma and surgery alone is suggested for melanoma. Therefore, the specific therapeutic approach varies depending upon the final diagnosis.

Lastly, the prognosis of all these lesions varies considerably. The five year survival figures are: melanoma 11%, embryonal rhabdomyosarcoma 12.5%, anaplastic carcinoma 25%–35%, esthesioneuroblastoma 52%, histiocytic lymphoma 50%–70%, and plasmacytoma 60%. The outlook of the physician, patient, and immediate family will vary markedly depending upon the diagnosis. Again, differentiation is far more than just academic.

Conclusion

The concepts presented here represent the growing fundamental role that the radiologist can

TABLE I

Tumor Type	Age	Location	Other
Embryonal Rhabdomyosarcoma	80% <12 years of age Most common malignant Soft tissue neoplasm of the head and neck in children	Nonspecific	
Esthesioneuroblastoma	70% 10–30 years of age	Upper 1/3 nasal cavity	
Plasmacytoma	40–70 years old	Nonspecific	10–30% have or will develop multiple myeloma
Histiocytic Lymphoma	60–70 years old	Nonspecific	
Melanoma	40–60 year old	lower 1/3 nasal cavity	
Anaplastic Carcinoma	40–60 years old	Nonspecific	

TABLE II

Tumor Type	EM	Stains
Embryonal Rhabdomyosarcoma	Myofilaments	Glycogen, Masson Trichrome
Esthesioneuroblastoma	Catacholamine granules	Formaldehyde induced fluorescence
Plasmacytoma		Methyl green pyronine (15% have amyloid) Congo Red
Histiocytic Lymphoma		
Melanoma	Melanosomes	
Anaplastic Carcinoma	Desmosomes	Reticulin stain

play in sinonasal malignancies. He can now direct the need for rebiopsy and electron microscopic and histochemical testing when the diagnosis of anaplastic carcinoma does not correlate with the roentgen picture. For the first time, based upon those results, the radiologist can direct the surgeon to operate prior to any adjunctive therapy in order to eliminate a coexistent mucocele.

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Gastrointestinal Abnormalities in the Cornelia de Lange Syndrome

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Abstract

The radiologic characteristics of Cornelia de Lange's syndrome have been well documented in the literature. We present four cases illustrating the radiologic manifestations of some of the less well described gastrointestinal anomalies associated with de Lange's syndrome. Our findings suggest a significant interrelationship among the feeding difficulties, vomiting, and recurrent chest infections present in this disorder and imply that the development of a hiatal hernia with gastroesophageal reflux culminating in esophageal stricture is an important clinical facet of this syndrome. We report the first use of a subcutaneous colon segment for esophageal bypass in a de Lange's syndrome patient. Consideration of the overall gastrointestinal picture is vital to provide the best possible care.

We dedicate this article to the festschrift in honor of Bernard S. Wolf, M.D., mentor, radiologist par excellence and, most of all, friend. We hope this article is fitting in view of Dr. Wolf's great interest and work in the gastrointestinal tract, especially the esophagogastric junction.

In 1933, Cornelia de Lange described two children with the syndrome that bears her name. To date, the number of reported cases exceeds 250 (1). The clinical manifestations of this congenital malformation syndrome include mental retardation and growth retardation in a low-birth-weight infant, generalized hirsutism, synophrys, long eyelashes and generalized microcephaly. The facies are characterized by anteverted nostrils, thin lips that are usually turned down at the angles of the mouth and a prominent philtrum. Hand abnormalities are frequent, with proximally placed hypoplastic thumbs and clinodactyly of the fifth finger. Extension and flexion may be limited at the elbows. There may be severe malformation of the upper extremities ranging from small hands to phocomelia. Cardiac defects are also common.

The radiologic characteristics of de Lange's syndrome have been recently well described by Peeters (2), whose study suggests, in agreement with the literature, that the radiologic changes apparent in Cornelia de Lange's syndrome cannot be considered pathognomonic, although the pattern profile of hand radiographs appears to be quite characteristic (3).

We have been impressed over the years by some of the less well described gastrointestinal changes manifested in de Lange's syndrome, and we present herein four cases that well illustrate the clinical and radiologic ramifications of the disorder.

Case Reports

Case 1 (PMB)

This female patient—the illegitimate product of mixed (Caucasian/Negro) parentage—was diagnosed as having de Lange's syndrome at age eight and one-half years. Birth, which occurred past term, was via spontaneous delivery to a mother who had severe toxemia (edema, hypertension with convulsions). The birth weight was 5 lbs. The child was first hospitalized at one month of age for feeding difficulties and fever. Even up to age eight and one-half years, the patient was unable to take solid foods, and feedings (by her grandmother) consisted primarily of baby food, that is, meats and vegetables mixed with milk in a bottle. The patient was hospitalized at age 14 for dehydration and vomiting, the etiology of which was believed to be an esophageal stricture associated

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with esophagogastric reflux. The child responded to intravenous (IV) fluid therapy and was discharged to be maintained on multiple small feedings. She was readmitted one month later with respiratory distress and swallowing difficulties. She was treated for left lower lobe pneumonia, probably secondary to aspiration, and discharged. Six months later, she was readmitted with fever, cough and vomiting; she apparently had again aspirated and had developed pneumococcal pneumonia. Following this discharge, the patient was lost to follow-up; it was later learned that she had moved to Hawaii.

Radiologic manifestations. Her skull films showed generalized microcephaly without hypotelorism. Films of the upper extremities revealed absence of the radius on the right with a hypoplastic deformed ulna and absence of the first ray and other digits of the hand. Films of the left upper extremity demonstrated dislocation and hypoplasia of the radial head with a thin but otherwise reasonably normal radius and ulna, a hypoplastic thumb and absence of several digits of the left hand.

A chest film, taken at age 15, revealed chronic lung changes due to multiple aspirations, more severe on the left than the right. There was marked nodularity in the left base with areas of atelectasis especially in the left lower lobe and lingular regions. Air trapping was marked.

A small bowel examination at eight years of age revealed no malrotation and a normal small bowel pattern. The spleen was somewhat enlarged; liver size was normal. Barium enema examination demonstrated no malrotation.

An esophagogram performed at age eight revealed evidence of cricopharyngeal abnormality with contrast medium entering the nasopharynx and, minimally, the trachea. The esophagus showed mild dilatation and absence of peristalsis. No hiatal hernia was demonstrable at that time. Gastroesophageal reflux was not looked for. A repeat esophagogram and upper gastrointestinal (UGI) examination at age 14 revealed a slightly improved swallowing mechanism with some mild residual cricopharyngeal abnormality but marked dilatation of the proximal and mid esophagus ending in an approximately 2 cm stricture of the distal esophagus associated with a small hiatal hernia (Fig. 1). Once again, esophageal peristalsis appeared to be absent.

Case 2 (MP)

At two weeks of age, this female patient was catheterized for congenital heart disease. Despite her multiple congenital anomalies, de Lange's syndrome was not diagnosed at that time. The patient was readmitted at age two and one-half years with pneumonia and seizures. At this admission she underwent ligation of patent ductus arteriosus. This patient was hospitalized many times both for her seizure disorder and also for episodes of milk curd aspiration and apnea (several times at two years of age) requiring mouth-to-mouth resuscitation. De Lange's syndrome was diagnosed at age two and one-half. She succumbed at age three and one-half years following a seizure, apparently associated with aspiration, and failure to respond to cardiopulmonary resuscitation.

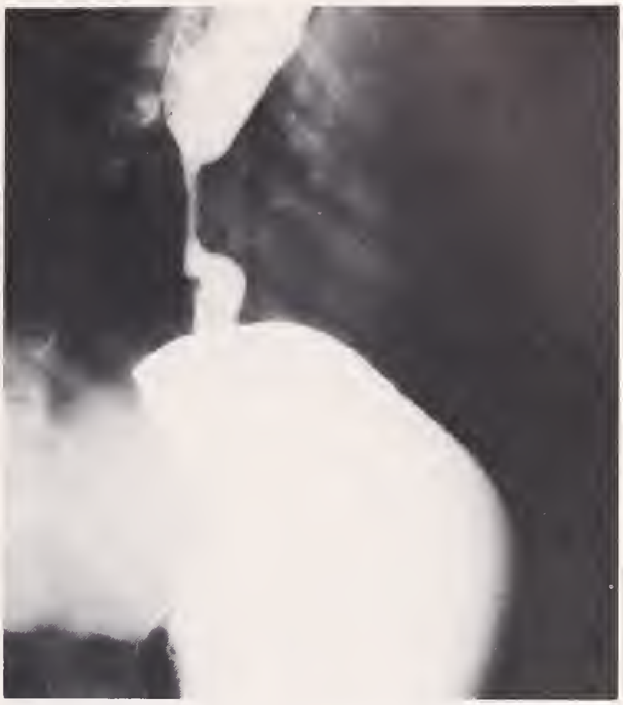

Fig. 1. Radiograph from an upper gastrointestinal series examination at age 14 years revealing atonic esophagus, distal esophageal stricture and small hiatus hernia.

Radiologic manifestations. This patient radiographically manifested mild microcephaly with minimal hypotelorism. Films of her hands reveal clinodactyly with a hypoplastic middle phalanx of the fifth finger and mild hypoplasia of the distal phalanx of the fifth digit. There is a proximally placed, not particularly short first metacarpal. There is, however, a deformity of the proximal metaphysis of the radius without subluxation.

An early urologic work-up provided poor visualization of the left kidney; however, a retrograde study revealed a reasonably normal left caliceal system and a normal right kidney. Chest films taken at two weeks of age demonstrated marked cardiomegaly with increased flow consistent with the catheterization diagnoses of patent ductus arteriosus with mild pulmonary hypertension and patent foramen ovale. By one and one-half years of age, the patient exhibited severe air trapping in both lungs with chronic changes present bilaterally, especially in the upper lobes.

An esophagogram performed at six weeks of age revealed no primary esophageal peristalsis and mild esophageal dilatation without hiatal hernia (Fig. 2). Secondary esophageal contractions were also present. The cricopharyngeal mechanism was not examined carefully.

Case 3 (RS)

This female patient—the third child of a gravida V, para 4, aborta 1 mother who was 24 years old at delivery—had a birth weight of 5 lb, 6 oz. Because of mild, episodic vomiting, the patient underwent an upper gastrointestinal (UGI) series at three and one-half years of age; Cornelia de Lange's syndrome was diagnosed at that time. A repeat UGI series was performed at age 12. Despite her multiple congenital anomalies and failure to thrive, this patient's clinical course has been reasonably benign.

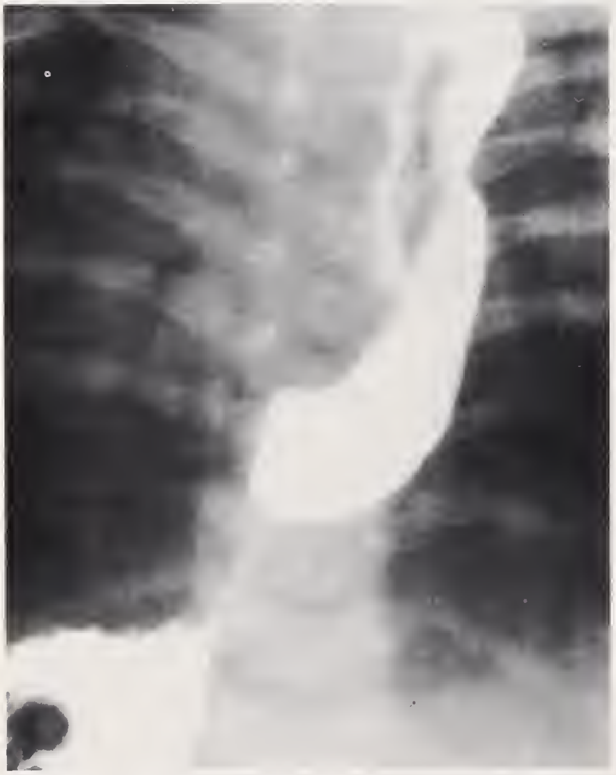

Fig. 2. An esophagram at six weeks of age revealing abnormal esophageal contractions and minimal dilatation.

Radiologic manifestations. An IV pyelogram demonstrated two normal kidneys and no renal anomalies. The small bowel examination showed no malrotation. A UGI series performed at age three and one-half revealed gastroesophageal reflux without a hiatal hernia; esophageal peristalsis was absent. Cricopharyngeal abnormality was noted, but there was no evidence of specific aspiration into the trachea. A repeat esophagogram performed at age 12 revealed significant esophageal dilatation with a small sliding hiatal hernia but no evidence of stricture (Fig. 3). Again, nasopharyngeal reflux was appreciated, but no definite aspiration into the trachea as the result of the cricopharyngeal abnormality was seen.

Case 4 (AH)

This male patient, whose birth weight was 5 lb, 3 oz, required resuscitation at birth. At that time, multiple congenital anomalies and unusual facies were noted. The patient spit up feedings and episodic vomiting began at three months of age. The diagnosis of Cornelia de Lange's syndrome was made at age four months. There was continuous failure to thrive from birth and the child weighed 16 lb at two and one-half years of age. At that time a UGI series was performed.

The child was placed in a private nursing home by the state at age five and one-half years. He weighed 22 lb at seven years, but his weight fell subsequently and he has never regained that

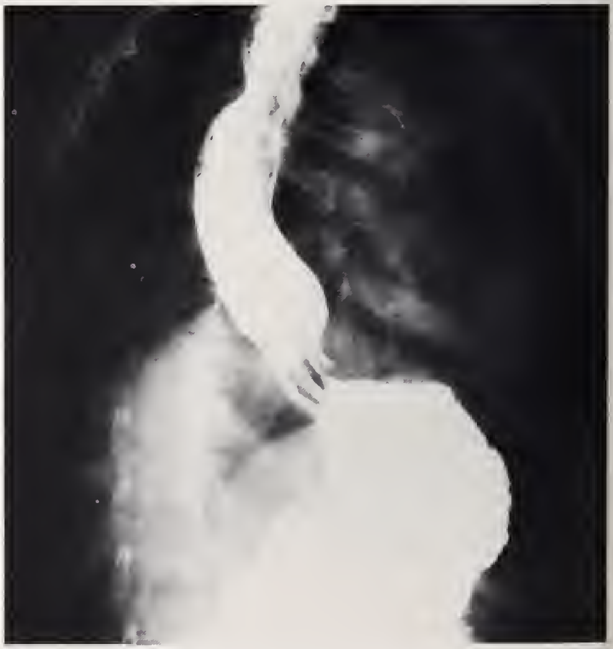

Fig. 3. An esophagram at 12 years of age revealing esophageal dilatation and absence of peristalsis.

weight. At age seven and one-half years he was hospitalized for four months because of weight loss and vomiting. On the basis of the UGI series findings, an esophageal bypass with a subcutaneous colon segment was performed. During the ensuing eight years, he has been admitted to the hospital 21 times. The nursing home records reveal that he is unable to retain oral feedings. On a recent hospital admission, at age 16 years, his weight was noted to be 15½ lb.

Radiologic manifestations. A UGI series performed at age two and one-half revealed free reflux of barium into the esophagus; this was noted by the instillation of barium into the stomach via nasogastric tube. This study also demonstrated 2 cm narrowing in the prepyloric area, suggesting either stricture or spasm. At age seven and one-half, UGI series and esophagogram revealed a severe, 3 cm distal esophageal stricture associated with a hiatal hernia (Fig. 4). The remainder of the esophagus was dilated and aperistaltic. An IV pyelogram in this patient demonstrated a crossed renal ectopia.

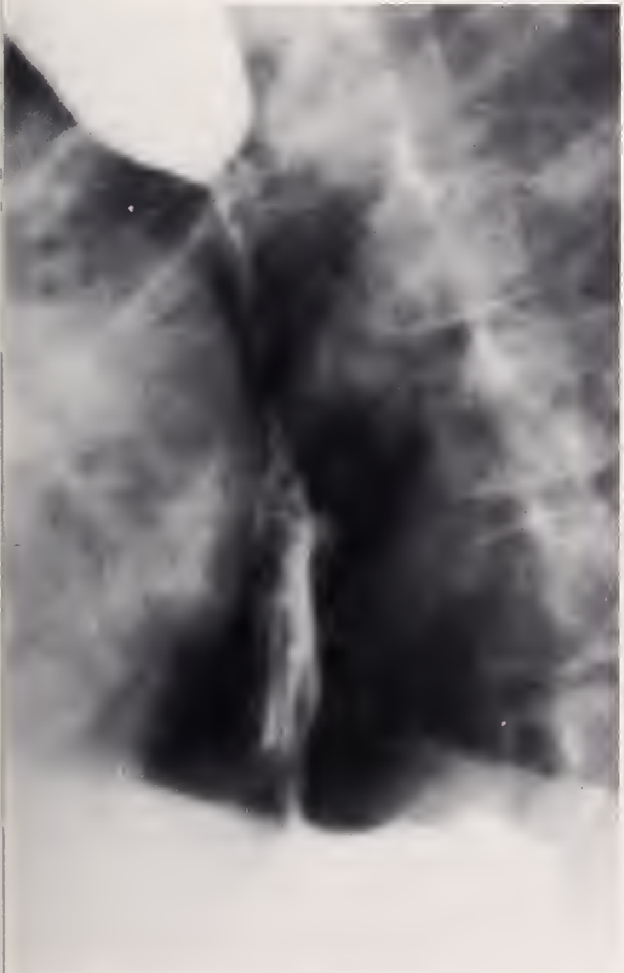

Fig. 4. An upper gastrointestinal series examination at age 7½ years revealing a stricture of the distal esophagus with hiatus hernia and proximal esophageal dilatation.

Discussion

This disorder was originally described by Brachmann as early as 1916 (it is also known as Brachmann-de Lange syndrome). Cornelia de Lange, a Dutch pediatrician, published her description of two infants with the disorder in 1933. In 1938 she reported a third case along with the postmortem findings (including gastrointestinal findings) of the first of her initial two patients (4). These gastrointestinal findings included malrotation with nonfixation of the duodenum at the ligament of Treitz and nonfixation of the colon in the right lower quadrant. The gastrointestinal anomalies were first emphasized by Schlesinger, who recommended barium visualization of the gastrointestinal tract in every patient (5). Significant gastrointestinal abnormalities associated with de Lange's syndrome can be found in Table I.

Although Mc Arthur and Edwards mentioned feeding difficulties, vomiting and recurrent chest infections, they did not discuss the possible interrelationship among the three (6). This relationship appears to have significance because, next to bronchopneumonia, gastrointestinal complications are the most common cause of death (1). Aspiration of specifically gastric contents has been reported in only three patients. The feeding difficulties and recurrent infections appear to improve after the age of two years although several patients, including one of ours, were unable to tolerate solid food until later childhood. This probably relates not only to the cricopharyngeal anomaly but also to the peristaltic abnormality that we have observed in these patients. Our case findings also imply that an important clinical facet of this syndrome is the development of a hiatal hernia with gastroesophageal reflux and ultimate progression to stricture of the esophagus; this observation is confirmed in the literature (2, 7). Although the progression of chalasia (gastroesophageal reflux) and resultant peptic esophagitis to severe stricture is not unique, it appears that our patient's colon replacement therapy (Case 4) has not been previously reported. There is no question that cricopharyngeal abnormality plays an important role in the recurrent infections and feeding difficulties seen in these children. We believe that consideration of the overall gastrointestinal picture is vital to providing the best possible care.

TABLE I

Gastrointestinal Abnormalities Reported in the de Lange Syndrome

1—Malrotation		
Previously reported (2,4–6,8–15)		21 cases
This study		0 cases
	Total	21 cases
2—Pyloric stenosis and/or duodenal obstruction		
Previously reported (10,16–18)		7 cases
This study		1 case
	Total	8 cases
3—Hiatus hernia		
Previously reported (one with stricture of esophagus) (2,7)		6 cases
This study (two with stricture of esophagus)		3 cases
	Total	9 cases
4—Other abnormalities		
Inguinal hernia (1,19)		15 cases
Umbilical hernia (1,20,21)		13 cases
Duplication (of colon) (5)		1 case
Meckel's diverticulum (6)		1 case
Perforation of gastric ulcer (1)		1 case

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Radiographic Findings Resembling Scurvy and Rickets in Prematures on Hyperalimentation

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Abstract

Seven premature infants presenting with metaphyseal alterations simulating features suggesting both scurvy and rickets are discussed. A common factor in all these infants was abnormal liver disease. Although similar radiographic findings can be encountered in other deficiencies, for example copper, the radiographic features and the fact that these patients did respond promptly to vitamin supplement suggests vitamin deficiency as the basis for their bone lesions.

Prematurity has always been recognized as a trying and difficult phase of life in which many organ systems can be harmed. Entities like hyaline membrane disease and idiopathic necrotizing enterocolitis afflict almost none but the premature. The bony skeleton is also not spared and the association of prematurity and rickets has been recognized for many years. To this, we wish to add a series of seven premature patients who demonstrated radiographic findings that simulated both scurvy and rickets. These infants were all cared for at the newborn center of the University of Tennessee.

Representative Case Reports

Case I

Girl MC was delivered at 32 weeks by elective C-section for Rh incompatibility after four intrauterine transfusions. Birth weight was 1570 gms; bilirubin total 17.3 mg%, and direct 10.8 mg%; Calcium 9 mg% and total protein 4.5 gm%. For the first week, the child was on peripheral alimentation with vitamin supplement and then oral feedings of similac 25. At one week the bilirubin had climbed to total 22 mg%, direct 16 mg%. The infant received several more transfusions for Rh incompatibility. At one month of age bony changes were noted on routine chest radiographs. One week later the child exhibited extreme irritability on being touched. This was felt to be consistent with the periosteal affects of scurvy. At six weeks of age vitamin C 100 mg and vitamin D 2,000 IU were started daily. There was subsequent gradual clinical and radiographic improvement. Other significant lab data: total protein ranged between 4.5-6.5 gm%; calcium was in the normal pediatric range; normal renal function.

Case II

Girl MA was born weighing 1230 gm. The infant had hyaline membrane disease and several episodes of staphylococcus sepsis. Multiple transfusions were necessary for hyperbilirubinemia and later anemia. By seven days of age the bilirubin was total 20 mg%, direct 15 mg%, SGOT was 270 units per liter. The infant was on peripheral alimentation for 14 days and by then the bilirubin was total 40 mg%, direct 28 mg%. Formula feedings were begun at this time, and at 21 days of age bone abnormalities were apparent on the radiographs (Fig. 1A). At 28 days, the bilirubin levels had dropped by half, and vitamin C 100 mg per day was started. At 38 days, the bilirubin was almost normal, and radiographically there was

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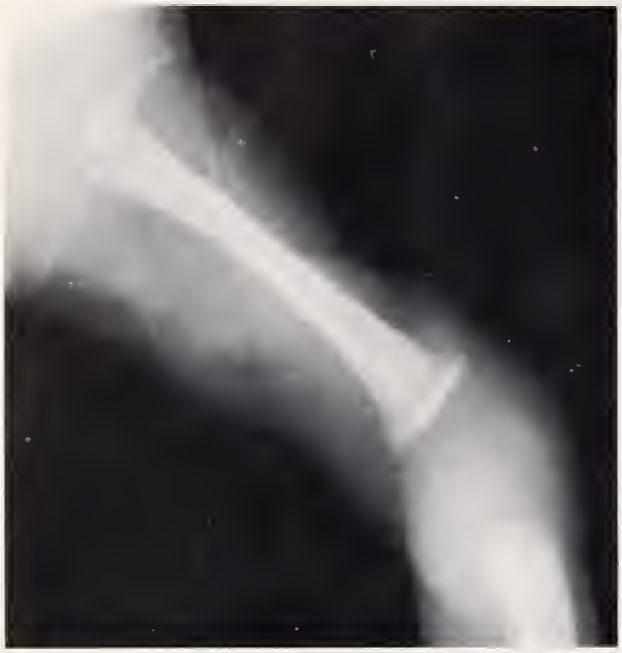

FIG. 1A. Case II. The distal femur demonstrates a dense zone of provisional calcification. The peripheral margin extends out beyond the shaft. A scurvy-like lucent area is present proximally.

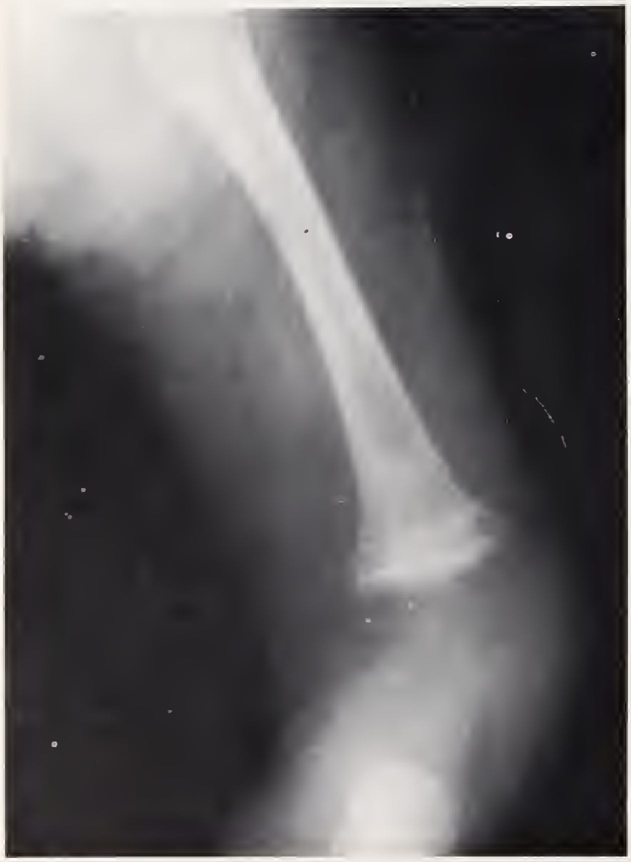

FIG. 1B. Following therapy with supplemental vitamin C, there is ossification of the metaphysis and a growth recovery line.

evidence of healing. During this entire period total protein remained at 5 mg%, and serum calcium was within the normal pediatric range.

Roentgen Manifestations

The composite radiographic features in these infants showed varying bony changes in the distal portions of the bones that resembled scurvy and rickets. In general almost all the long bones were involved. However, in some patients the findings were initially observed on routine or serial chest examinations, and in these only the humeri were available for examination. The early change noted in the majority of the patients was an increase in density in the zone of provisional calcification. This zone is normally smooth but appeared somewhat irregular and extended beyond the peripheral margins of the bone into the surrounding soft tissues. A prominent lucent zone was also present immediately adjacent to the epiphyseal line (Fig. 1A). In others, rachitic alterations were more obvious. At the time of discovery the bones in these infants demonstrated complete absence of the epiphyseal line. This was replaced by an irregular dentate zone that in some patients was distinctly splayed and separated from the adjacent epiphysis. (Fig. 2) The bony trabecular structure in these cases appeared

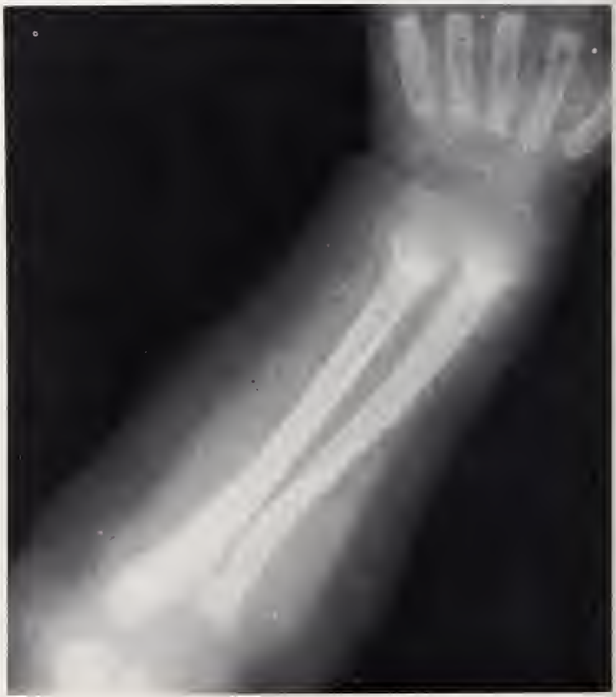

FIG. 2. Case VI. Metaphyseal cupping and loss of the zone of provisional calcification is noted in the radius and ulna. The findings resemble rickets.

coarse. Since adequate serial studies were not available in our patients, it is difficult to denote whether these changes represented two distinct entities or whether they represented a continuum of disease. Two of the infants demonstrated other radiographic findings at times noted in scurvy. One showed epiphyseal slippage (Fig. 3A) and the other prominent metaphyseal notching (Fig. 4A). Poor bony mineralization was apparent in several infants.

Resolution of all the above findings was encountered in the patients who survived their underlying disease. This became apparent approximately two to three weeks after treatment with vitamin supplements was initiated (Figs. 1B & 3B). The initial response occurred primarily in the zone of provisional calcification which became thicker and more dense. At the same time, the margin appeared smoother. Zones of ossification appeared to extend through the adjacent lucent zone to connect the epiphyseal growth line with the metaphysis (Fig. 4B). These bony bridges probably indicate an irregular pattern of bone formation.

Periosteal reaction along the shaft was also noted in one case. This was spotty and amorphous and was probably caused by subperiosteal hemorrhage (Figs. 4B & 4C). The extreme tenderness noted on palpation was consistent with this finding. Bone healing represented by either unilaminar or multilaminar periosteal deposition was not apparent. However, asymmetrical periosteal deposition at the site of epiphyseal slippage was also noted in two patients.

Discussion

Although the specific diagnosis of scurvy and/or rickets could not be completely confirmed clinically in our patients, many of the radiographic features noted in these patients resembled those encountered in these disorders. The appearance of true rickets and even more so scurvy in the premature is strikingly unusual. In fact, it had been believed that infantile scurvy never occurred below three months of age, and that reported cases of this entity in this age group were attributable to congenital syphilis (2). Nevertheless, one well documented case of infantile scurvy has been recorded. This occurred in an eight-week-old infant being fed nonvitamin fortified formula, no solid food, and no juicies (1). Despite some contention that this may have been a case of battering (2), response to ascorbic acid was dramatic.

Rickets of the premature based on the presentation of metaphyseal lucent bands was at one time a fairly popular diagnosis. However, the deposition of minerals that occurs maximally during the third trimester is impeded by premature birth. Eek et al (3) have demonstrated that this form of demineralization is a normal physiologic occurrence and not rickets. It is very unusual to find rickets on a nutritional basis below two months of age.

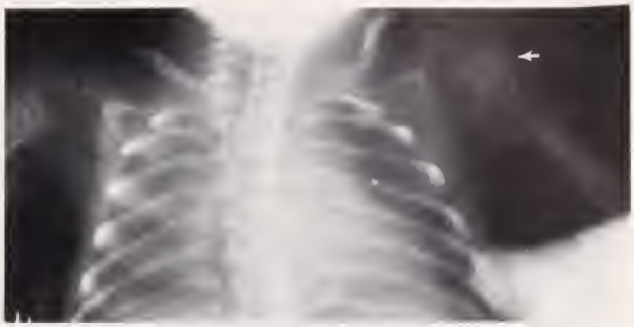

FIG. 3A. Case IV. The proximal humeri are severely irregular. The zones of provisional calcification are serrated and dense. An impression of epiphyseal slippage is present as indicated by asymmetric periosteal deposition (arrow).

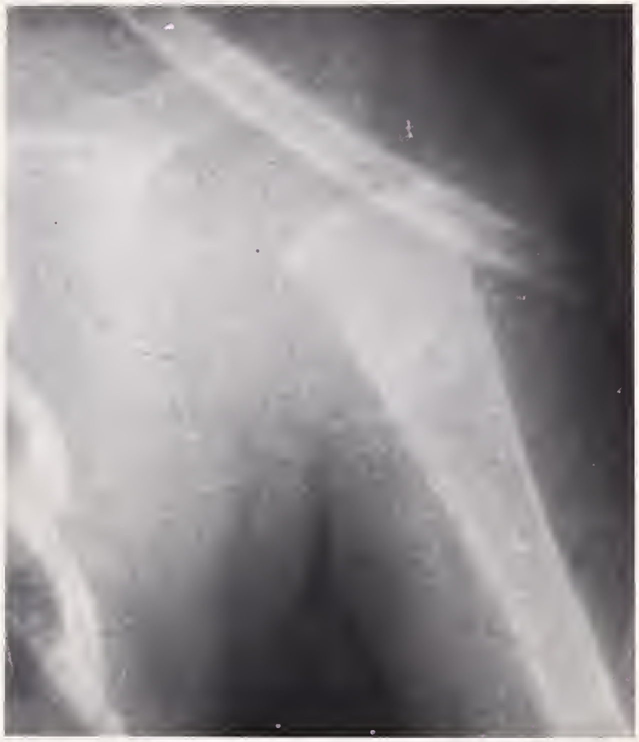

FIG. 3B. Complete resolution is apparent one month after supplementary vitamins C and D had been instituted.
Case I
Metaphyseal notching (arrow) and irregular margins—findings.

There are several factors that must be considered in the development of nutritional deficiencies in the seven prematures encountered. Most significant is that each infant had severe

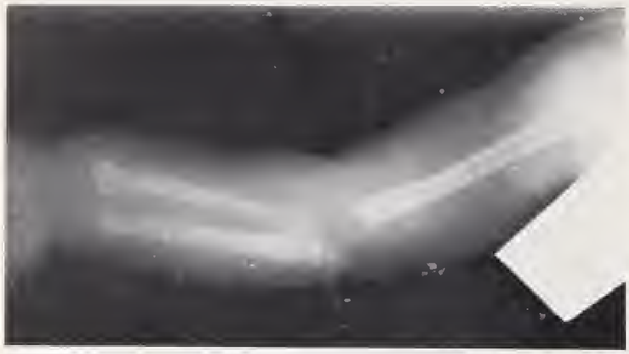

FIG. 4A. Three weeks after metaphyseal notching and irregular margins were noted in the proximal humerus but after only one week of supplemented vitamins C and D, the findings have progressed. Now the metaphyses are all dense and thick but with some apparent bony bridging extending across the adjacent lucent zone. Periosteal changes are also present.

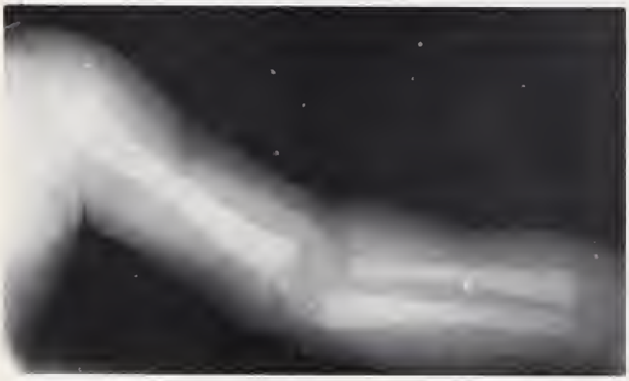

FIG. 4B. The other arm better demonstrates the amorphous periosteal reaction.

neonatal liver disease with prolonged elevated bilirubin, both direct and total at one time or another. In five patients, liver disease as evidenced by elevated bilirubin was apparent at the time the bony abnormality was present. In the remaining two patients, the bilirubin levels were normal although they had been recently elevated (Table I). The cause of hepatic damage was not always clear although these infants often required multiple antibiotics for sepsis and transfusions for anemia.

TABLE I
Roentgen Findings and Liver Abnormalities

Case	Baby	Age at First Roentgen Findings	Bilirubin (direct/total) at first Roentgen Findings
I	MC	4 weeks	5/8 mg%
II	MA	3 weeks	23/31
III	SC	13 weeks	5/6
IV	KE	5 weeks	normal*
V	HA	8 weeks	normal**
VI	BR	6 weeks	11/21
VIII	GR	11 weeks	13/18

* For first 3 weeks bilirubin was 1–3/4–10
** At 6 weeks bilirubin was 6/10

Another common factor was that all infants were on hyperalimentation probably containing an inadequate amount of vitamin supplements. When receiving peripheral alimentation, prematures under 1500 gm were given a supplement of 50 mg ascorbic acid and 100 IU ergocalciferol, vitamin D2. After being switched to formula, they received standard Similac formula with no additional vitamins. For 1500 gm infants taking only 200 cc/day, this amounted to 10 mg ascorbic acid and 80 IU cholecalciferol, vitamin D3, daily.

The necessary amount of vitamins required for premature infants is unknown. Prematures have rapid bone development and can no longer depend on the maternal circulation for their increased nutritional demands. Although 10-20 mg of vitamin C daily is presumably adequate for adults and is the accepted requirements for children, absolute requirements for prematures are unknown (4–5). In addition, the measurements of serum ascorbic acid in an infant already receiving more vitamin C is not significant since it corresponds only to the dietary intake of the vitamin and not to the total body amount available to the infant (9). The amount of vitamin C that a mother receives prior to delivery may afford the infant some temporary protection. In this respect one mother (baby MC) did actually have a very low serum ascorbic acid.

The changes resembling rickets in these infants may be due to a variety of reasons. These prematures were receiving either vitamin D2 100 IU daily intravenously or vitamin D3 80 IU daily as part of their formula. This is below the usual daily requirement of 100–200 IU for infants but may be adequate for most small healthy neonates (4). However, all our patients had liver disease and liver stasis. Both of these processes can contribute to abnormal Vitamin D metabolism. Liver disease probably impedes the hydroxylation required by the vitamin before it reaches the kidney for activation. In addition, liver stasis results in diminished bile acid secretion into the small bowel. Bile secretion is responsible for fat absorption which is subsequently reduced along with vitamin D3, a fat soluble vitamin, in the infant's formula. So in effect, both absorption and metabolism of Vitamin D were interfered with. Similar bony findings may be encountered in biliary atresia and other causes of biliary obstruction (8, 10).

It is not certain why the radiographic pattern in a given case more closely resembled scurvy and in another rickets. It may well be that we are dealing with a combined nutritional deficiency and that either may be the dominant factor radiographically.

Other incalculable factors that may play a role include hypoproteinemia, sepsis, anemia, and electrolyte imbalance. The immaturity of the gut also limits absorption of the orally given vitamin to some degree.

The above described features are also somewhat similar to those found in the premature infants presented by Griscom et al. A nutritional or metabolic etiology was suggested as was the possibility of copper deficiency. The latter also presents with similar bone changes, neutropenia and anemia. However, these infants as did ours, recovered on added vitamin C and D without additional copper.

Iatrogenic rickets in low birth weight infants is not unknown and has been reported. (7) Recently one such case came to our attention from an outside institution. The etiology in this infant was obvious and quickly corrected. The pharmacy was preparing the peripheral alimentation fluids by the liter, and the vitamin supplement was being calculated inadvertently on the presumption of fluid intake of one liter per day. The patient however was receiving only a small fraction of this liter and its vitamins per day. This problem nevertheless bears striking similarities to the seven infants presented. In the last case, miscalculation accounted for the inadequate amount of vitamin supplement.

It is conceivable that deficiences in other nutrients may be responsible, but all improved on high doses of vitamins C and D. In addition, the infants maturing, were able to take more formula, and demonstrated improved liver function. It is conceivable that all these factors contributed to improve the existing nutritional status.

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Computed Tomography in Diagnosis of Vascular Rib Lesions in Children

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Computed tomography with and without contrast was utilized to evaluate several pediatric patients with rib tumors. Two patients with tumors of the rib showed extreme vascularity with contrast enhancement. This suggests that the diagnostic information obtained from the computed tomography scan is useful in surgical planning. Two cases of posterior rib lesions, a hemangioma and an aneurysmal bone cyst presenting as incidental findings on routine radiography, were examined by conventional tomography and computed tomography with and without contrast. Both lesions had marked enhancement when contrast was given, suggesting the diagnosis and also alerting the surgeon to anticipate a fair amount of bleeding at surgery.

Case Reports

Case 1: A 12-year-old female was admitted to The Mount Sinai Hospital with a large lesion of the right posterior 5th rib found incidentally on a chest examination one month prior to admission. When only one day old, she had developed cyanosis and had been found to have transposition of the great vessels with dextrocardia, pulmonary artery stenosis and a single ventricle. At 36 hours of age, she had had a Blalock-Taussig procedure and at five years of age, a Glenn procedure was performed through a right thoracotomy without complications. The patient was fluoroscoped yearly by her cardiologist but no chest radiographs were obtained until one month prior to admission when she developed an upper respiratory infection and a chest x-ray revealed a posterior mass.

Repeat PA and lateral chest radiographs on admission showed that the lesion arose from and expanded the posterior aspect of the 5th rib with a coarse trabeculated appearance (Fig. 1A, B). Computed tomography without contrast (C−) confirmed the large mass and showed the expansion of the contours of the rib with perpendicular bone spicules within the mass (Fig. 2A). Computed tomography studies with contrast (C+) of the rib showed dramatic contrast enhancement of the entire mass which was confirmed by a marked increase in the attenuation coefficient (Fig. 2B). Both C− and C+ studies also showed that the lesion, although basically located in the most posterior portion of the rib, had no sharp zone of demarcation suggesting that the posterolateral aspect of the rib might be involved as well.

At surgery, the patient was put in a lateral position with the right side up and the old incision was excised and extended in a hockey stick fashion posteriorly and superiorly. The mass arose from the right 5th rib posteriorly bulging into the chest with intact pleura over it. It was necessary to remove the 5th and 4th rib en block since the 4th rib was very close to the mass and the prior surgery had apparently been carried out through the 4th intercostal space. Therefore, there was some scarring and periosteal new bone formation in the form of bulging between the 4th and 5th ribs. In the process of removal, there was considerable bleeding and severe oozing and it was necessary to replace blood loss with four units of whole blood.

X-rays of the specimen revealed the presence of abundant trabecular bone between the engorged vascular spaces (Fig. 3).

The pathology report indicated a large expanding hemangioma of the 5th rib with no evidence of malignancy. However, the tumor was also present in the lateral resected end of the 5th rib. The patient did well postoperatively and is being followed for recurrence.

Case 2: A 14-year-old male was admitted to The Hospital for Sick Children with a left thoracic mass discovered on a routine radiograph. The x-ray revealed a sharply demarcated cystic expansile lesion arising from the level of the 5th rib, almost at the vertebral junction (Fig. 4). Com-

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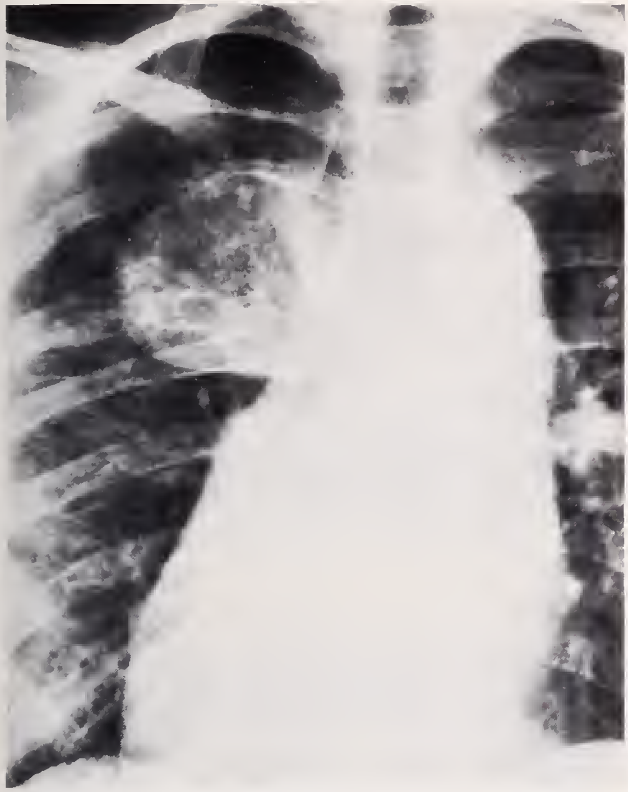
FIG. 1A. Frontal chest radiograph shows an expansile mass arising from the right posterior 5th rib with a disorganized trabecular pattern in a patient with dextrocardia.

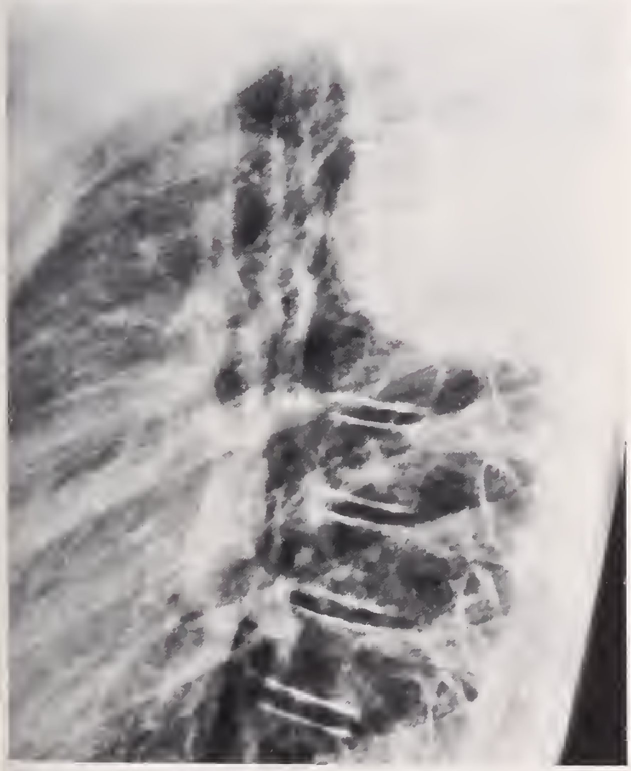
FIG. 1B. Lateral radiograph demonstrates the extreme posterior location of the mass as well as its extrapleural location.

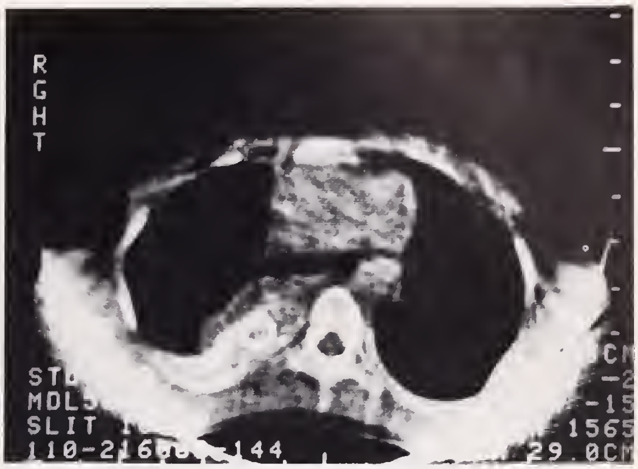

FIG. 2A. A representative CT image without contrast shows the trabeculae extending perpendicular from the mass.

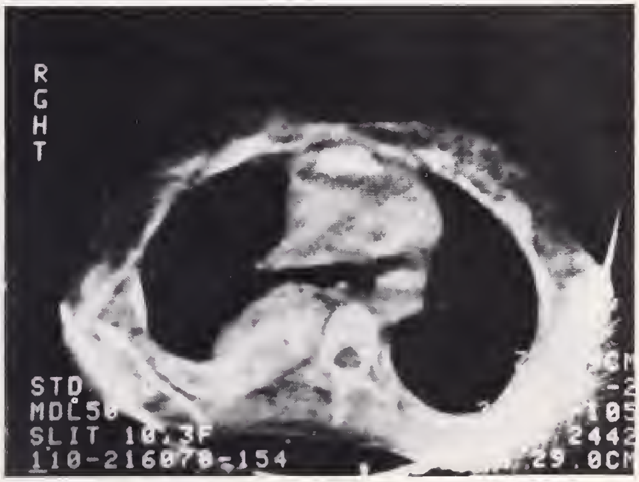

FIG. 2B. Marked contrast enhancement within the mass is visualized on the C+ CT scan.

puted tomography without contrast (C−) confirmed the destructive expansile cystic lesion in the posterior aspect of the 5th rib with a few bony septae within the lesion (Fig. 5A). Striking enhancement of the internal matrix of the lesion occurred after contrast was administered (Fig. 5B) and the preoperative diagnosis was that of an aneurysmal bone cyst.

At surgery, a left posterolateral thoracotomy was performed and the lesion was cystic arising in the left rib ending very close to the neck of the rib. While dissecting off the cyst, the cyst was inadvertently entered and a fair amount of bleeding was encountered, particularly in the center. The bleeding took a certain amount of time to control using both pressure, bone wax, and Gelfoam. There was also bleeding from the soft tissue at the edge of the lesion controlled mainly by cautery. The gross specimen consisted of rib measuring 7 × 15 × 1 cm and at the end of the specimen there

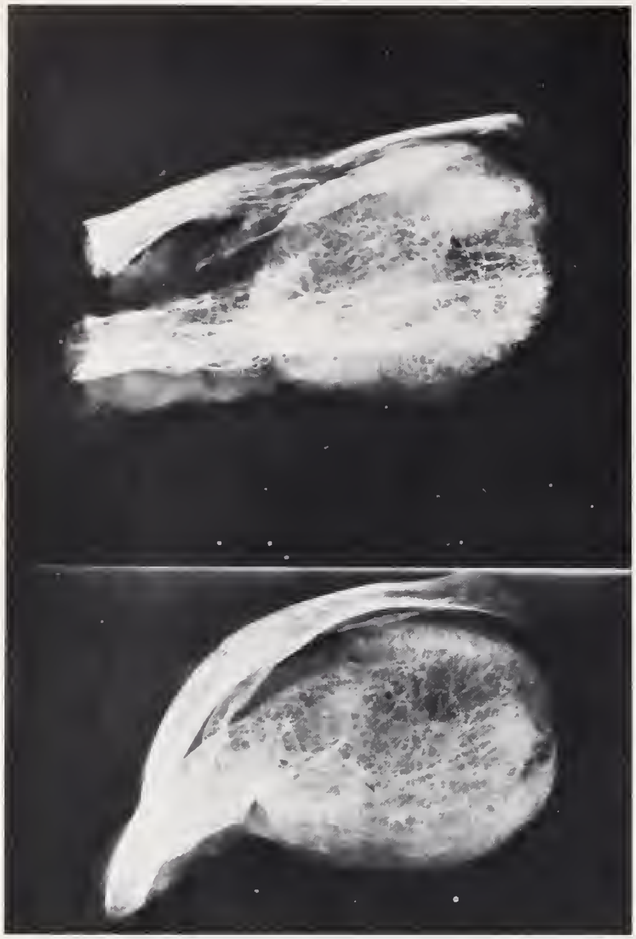

FIG. 3. Roentgenograph of the specimen shows the multiple coarsened trabeculae surrounding vascular channels.

was a mass covered by thin bone cortex containing blood clot and bony trabeculae. Microscopic sections of the bone were consistent with aneurysmal bone cyst. The patient had an uneventful postoperative course.

Discussion

Hemangioma is a true primary bone tumor of vascular origin (1). However, primary aneurysmal bone cysts are defined histologically as anastomosing fibrous-walled channels containing blood. These channels may have a complete or incomplete lining of endothelial cells but, unlike true blood vessels, they contain no elastic lamina or muscle layer (2). Of particular interest is that a few tumors diagnosed as hemangioendotheliomas were later reexamined pathologically and judged to be aneurysmal bone cysts (1) suggesting that the differences between true vascular bone tumors and aneurysmal bone cysts may be minimal. Therefore, it is of no surprise that both tumors may bleed extensively during surgery and a preoperative diagnosis is helpful in surgical planning. Aneurysmal bone cysts, as is well known, are now classified as either primary or secondary, the latter referring to the findings of a coexistent lesion (2). Our case was the primary or simple aneurysmal bone cyst with no complicating features.

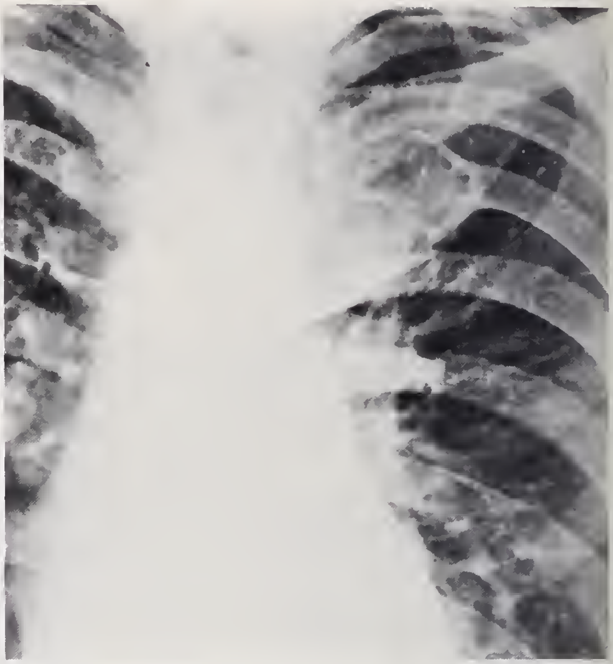

FIG. 4. Closeup of a frontal chest radiograph shows an expansile well marginated mass arising from the left posterior 5th rib.

Hemangiomas of the rib are exceedingly rare (1, 3); aneurysmal bone cysts of the rib are more common although again this is an unusual location (4). Both lesions expand the contour of the bone with cortical thinning. Most aneurysmal bone cysts show septation while hemangiomas tend to show coarse radiating bone trabeculae. Angiography of both these lesions usually shows staining and pooling of contrast medium within the lesion but now with the advantages of computed tomography, the vascular nature of these tumors as well as their extent can be easily delineated with contrast enhancement. Other lesions that were studied by computed tomography, including osteoid osteomas, fibrous dysplasia, nonossifying fibromas, enchondromas and metastatic neuroblastoma (5), did not enhance significantly after contrast was administered.

Computed tomography was very important in both establishing the extreme vascularity of these masses as well as the bone changes within the

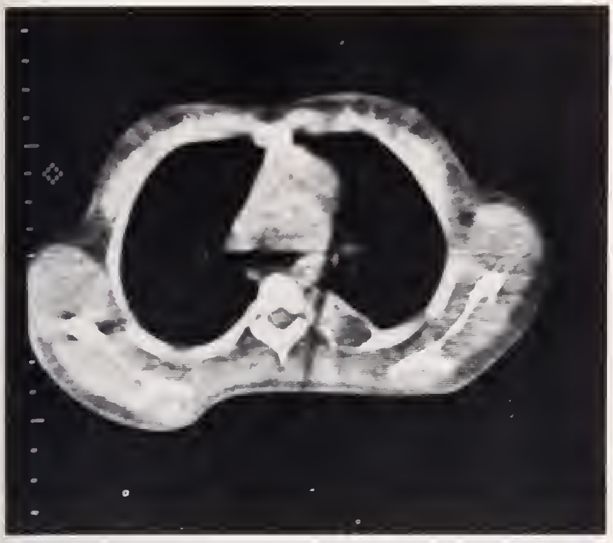

FIG. 5A. Without contrast the CT scan demonstrates a cystic expansile lesion arising posterior from the left 5th rib.

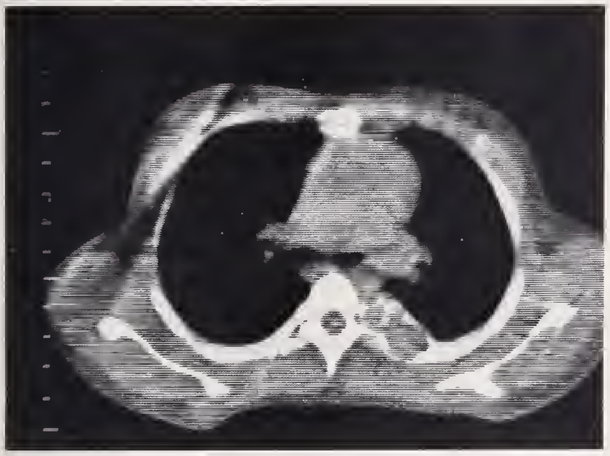

FIG. 5B. With contrast the rib mass becomes extremely vascular internally and the cortical erosion is well demonstrated.

masses. Before CT was available, angiography would have been necessary to demonstrate the extreme vascularity of these and other lesions. By the use of pre- and postcontrast CT scanning, the need for angiography has been to a great extent obviated. CT was also valuable in determining intraosseous extent of the disease as in Case 1.

In trying to relate the development of the hemangioma to previous trauma in a patient with prior surgery involving an adjacent rib and a large scar overlying the lesion, we could find no firm evidence that hemangiomas are posttraumatic in origin. Dr. S. Von Krepp (6) in 1965 reported a single case of a hemangioma of the lower tibia diagnosed after the patient had trauma to the ankle. However, the history suggested that the ankle was swollen previous to the trauma and therefore the hemangioma was most likely a preexisting lesion.

In conclusion, computed tomography of a rib lesion is not only a simple procedure, but adds valuable information in expansile tumors of the ribs.

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Uses and Limitations of Computerized Tomography of the Pelvis

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Introduction

Computerized Tomography (CT) is a reliable means of identifying pathologic entities involving the male and female genitourinary tract organs, rectosigmoid, and pelvic wall structures. Once the normal anatomy has been learned in axial presentation, abnormalities are generally easily visualized which may confirm findings present on physical exam, plain films of the abdomen, IVP, or barium studies (2). Various techniques of identifying hollow viscus structures have been reported and are easily used in a busy CT department (6). Localization and extent of disease are frequently the major tasks, with which the clinician needs assistance. A histologic diagnosis is often not possible and pathologic diagnosis is still necessary in most cases.

Materials and Methods

CT pelvic examinations were performed on a General Electric 8800 CT/T scanner approximately one hour after oral ingestion of 24 ounces of Gastrografin 3% mixed with water and orange flavoring. Scans were obtained at 1 cm or 2 cm intervals starting at the symphysis pubis and ending at the iliac crests. Recent addition of the GE Scout View enables fewer tomographic cuts to be obtained at the correct level when indicated. Identification of the rectum and sigmoid was generally very easy because of the predicable location of these structures and the contents within the lumen consisting of gas, fecal material which often contains Houndsfield numbers in the range of fat and gives a characteristic bubbly appearance, or by residual barium from prior studies. Occasionally, gas-barium interface may cause problematic artifacts.

In many patients a tampon within the vagina clearly indicated the presence of that structure and the approximate location of the cervix (4). Unopacified urine within the bladder is the most useful "contrast agent" necessary in the urinary bladder. When a Foley catheter and balloon are present or following and IVP or cystogram, contrasts within the bladder may be helpful; however, if the contrast is too concentrated, disturbing artifacts will result. Fat density fills in the surrounding organs and muscle, vascular and nodal structures along the pelvic walls adjacent to the bones. Asymmetry of both sides of the pelvis is also very helpful to establish unilateral abnormalities (5). Infusion of intravenous contrast material is occasionally helpful in delineating vessels and differentiating fluid filled masses from vascular structures or neoplasms.

Results

A total of 55 CT pelvic examinations was performed in eleven months. In 15 patients, normal anatomic structures were visualized or expected postsurgical absence of various organs was demonstrated. The remaining 40 cases revealed various pathologic entities which are listed in Table I.

Discussion

Postoperative Examination: CT of the pelvis is very helpful in the postoperative search for residual or recurrent neoplasm to determine whether the patient requires additional radiation or chemotherapy. Complications following surgery have been noted on CT. By use of the Houndsfield numbers a lymphocele may easily be detected and differentiated from a neoplasm since it contains water density fluid (Fig. 1). Abscesses in the area of surgery or loculated ascites can be differentiated from pelvis mass of neoplastic origin (9). Hydronephrosis is a frequent finding if one performs additional slices in the region of the kidneys in patients with known gynecologic tumors.

Carcinomas of the cervix and uterus in our experience have been indistinguishable and pathologic biopsies are required for histology and grad-

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TABLE I

Pathologic Diagnosis of Pelvic CT in 55 Cases

Normal	12
Post surgical change	3
CA cervix	4
CA endometrium	3
Uterine fibroids	2
CA ovary	6
Hodgkins disease (lymphoma)	3
CA colon	4
Diverticulitis	1
Prostatitis	1
CA prostate	2
Metastatic mass	5
Bladder stones	1
Bladder diverticulum	1
Bladder tumor	5
Lipoma of pelvis	1

ing. There is no question however of the value of CT in confirming the presence of a mass to begin with, and once a positive biopsy has been obtained, use of CT for the extension of carcinoma to surrounding organs for staging purposes is well documented (8). Follow-up examinations for effect of treatment on tumor is also useful (Fig. 2). When a cleavage plane between the uterus or cervical mass and the urinary bladder, rectum or sigmoid is unable to be found, it must be presumed that these organs are invaded and confirmation by means of barium enema and cystogram may be indicated (Figs. 3, 4). We have had difficulty distinguishing uterine fibroids or metastatic disease to the region of the cul-de-sac from primary cervix or uterine neoplasms since these entities create similar images.

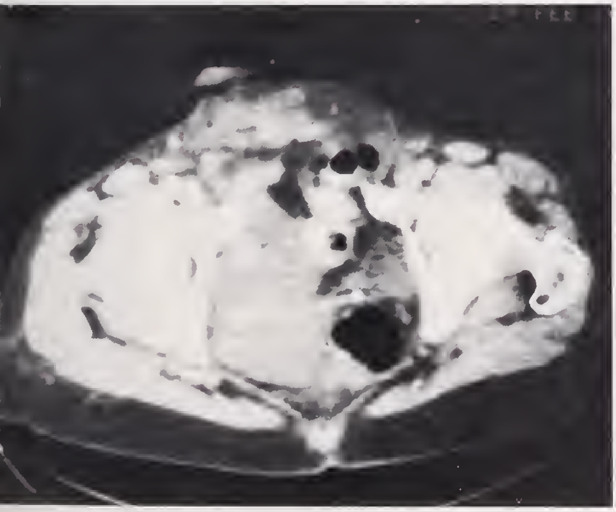

FIG. 1. Lymphocele—Water density (right) pelvic mass following hysterectomy. No further procedure required.

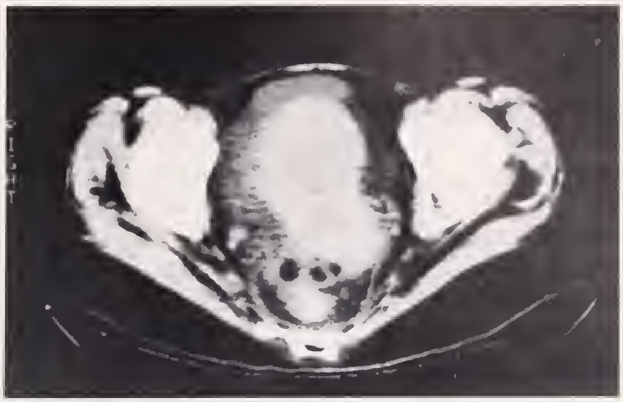

FIG. 2. Carcinoma of Cervix— This enlarged uterus could represent a leiomyoma except for extension into (right) pelvic wall.

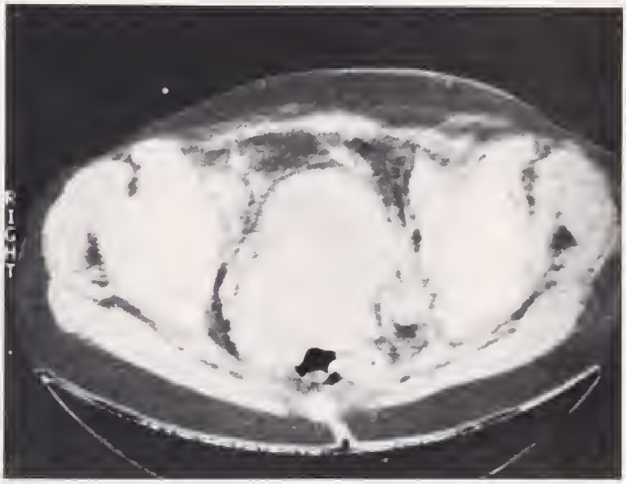

FIG. 3. Large mass between rectum and bladder is an anaplastic carcinoma involving the cervix and bladder. Note (left) iliac adenopathy.

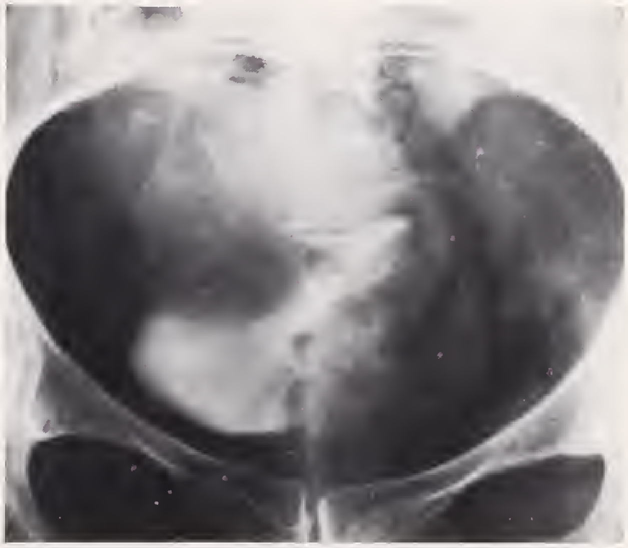

FIG. 4. Same case as Fig. 2— the urinary bladder is markedly distorted by tumor invading the left lateral wall. Compare this to bladder wall thickening on the CT study.

Carcinoma of the ovary is a difficult diagnosis to make because of the small size and varying locations of the normal ovaries. Many of our normal female pelvic scans were follow-up examinations in patients that had had total abdominal hysterectomy and bilateral salpingo-oophorectomy. In the patients in whom positive biopsies have been obtained, the extent of the pelvic mass, presence of ascites, mesenteric implants, hydronephrosis due to ureteral compression, and the presence of bone metastases may all be detected by CT examination. Rather than subjecting the patient to multiple radiologic examinations, CT might be the first examination to be used with the use of additional studies deferred until later symptoms arise (Figs. 5-8).

Masses in the presacral area and cul-de-sac may cause confusion because of adherence or invasion of adjacent gynecologic organs. If a fascial plane between mass and normal uterus and rectum can be made, additional studies may not be required. The histology is unpredictable except in the cases of fluid or fat filled structures such as lipomas, dermoids or possibly an anterior meningocele (Figs. 9, 10) (1).

Bowel Lesions: Diverticulitis with uterine perforation in one of our patients presented with the appearance of an irregular inflammatory mass which fused a shaggy outline of the sigmoid colon and the uterus (Fig. 11). The differential diagnosis must include a primary carcinoma of the colon or a uterine carcinoma with a colon perforation. With more experience, the preoperative diagnosis of diverticulitis might be more readily made in future cases. We have had the opportunity to examine one patient with a high rectal carcinoma which was found on emergency barium enema

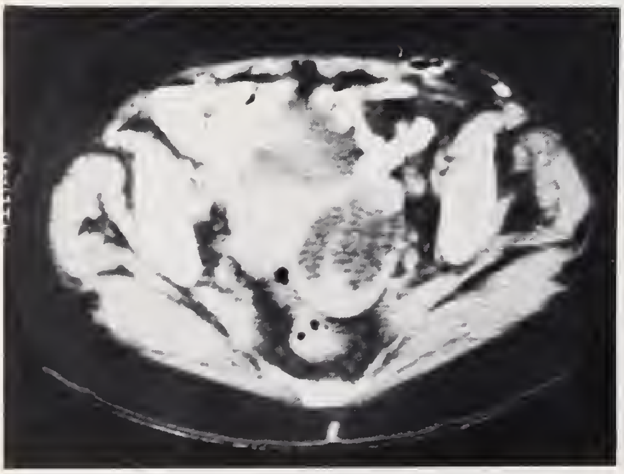

FIG. 5. CA ovary— A 6-8 cm mass is noted in the left adnexal region containing mixed densities, well circumscribed and no evidence of metastases.

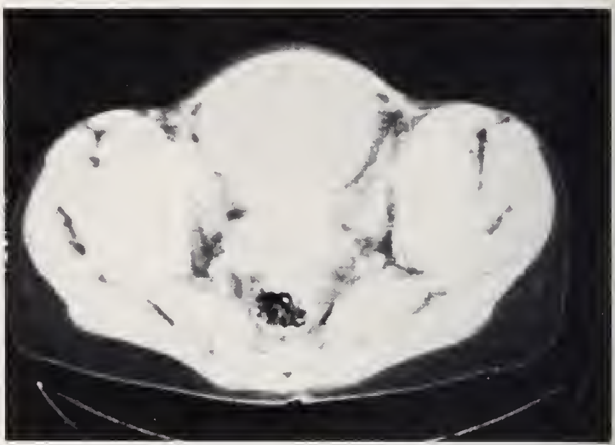

FIG. 6. CA Ovary— This slice is just above the urinary bladder and demonstrates ascites which has loculated anteriorly. The uterus is enlarged. The ovary could not be identified.

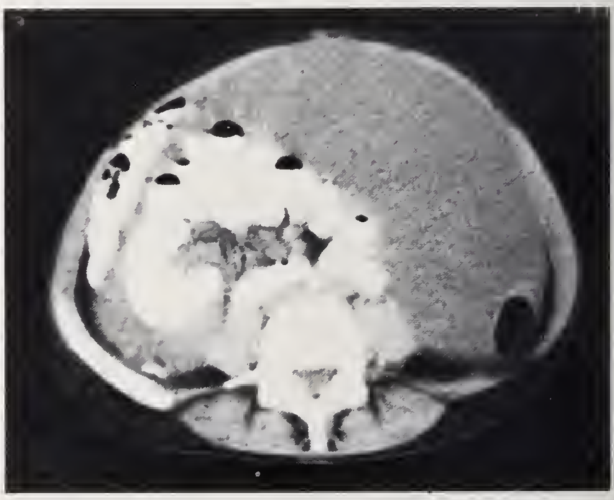

FIG. 7. CA Ovary— Same patient as Fig. 6. Ascites in midabdomen deviates gastrografin filled small bowel loops and surrounds lower edge of liver.

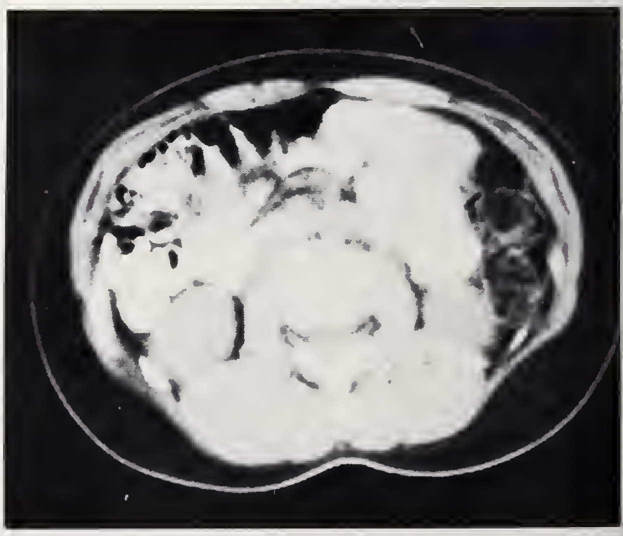

FIG. 8. CA ovary with metastatic deposits in the mesentery seen on the right side sharply indenting small bowel loops containing gastrografin.

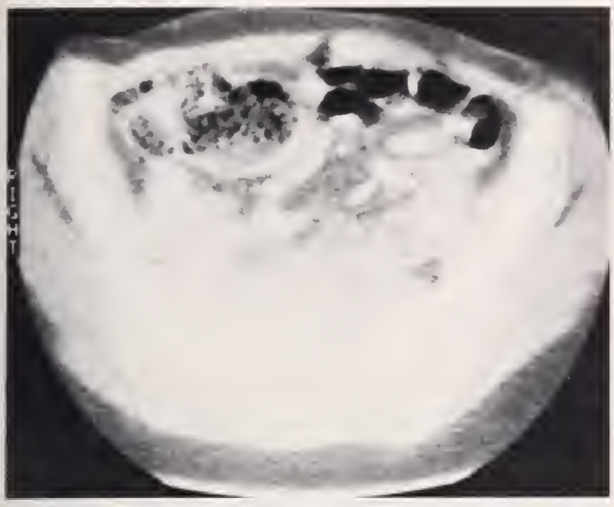

FIG. 9. Hodgkins Disease involving the left sacrum. Note bone destruction and large soft tissue mass projecting anteriorly which could not be appreciated by any other modality.

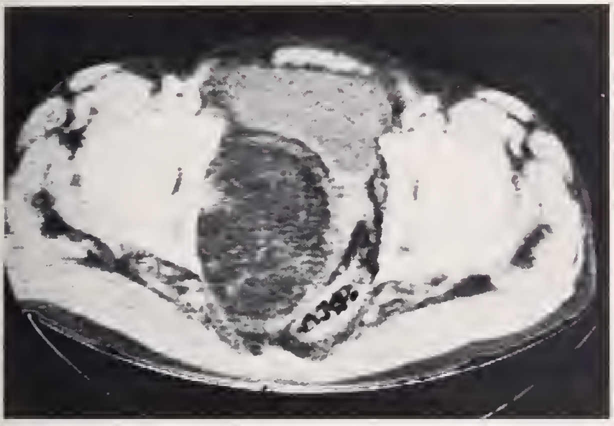

FIG. 10. Lipoma – Large (right) pelvic mass compresses all pelvic structures and caused sensation of pressure in this patient. Biopsy revealed no evidence of malignancy and confirmed presence of fat indicated by CT number-44.

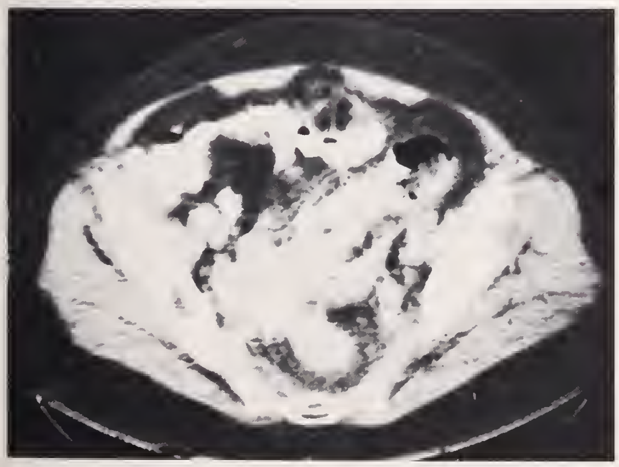

FIG. 11. Diverticulitis involving the sigmoid colon with perforation into uterus. The sigmoid wall is very thick and irregular with surrounding inflammatory reaction.

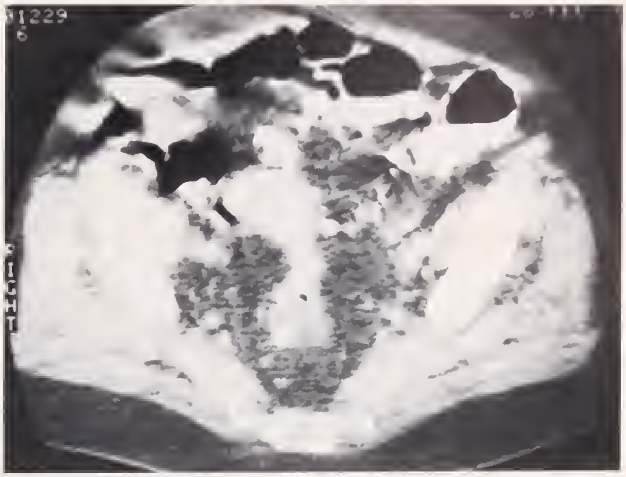

FIG. 12. CA Rectum – Narrowed lumen and thickening rectal wall is seen corresponding to pathologic specimen. No involvement of the serosa or evidence of metastatic nodes.

and appeared as a typical "apple core" lesion. Prior to surgery, the CT revealed lack of a bulky mass surrounding the narrowed lumen (10). The findings in this case showed that there was thickening of the rectal wall which occurred primarily from the serosal level inwards towards the lumen without much bulging or extension into the surrounding fatty soft tissues. This lesion was resectable at surgery and no extension beyond the serosa or metastatic lymph nodes were encountered (Figs. 12, 13).

Prostatic carcinoma has a CT appearance indistinguishable from prostatitis or benign prostatic hypertrophy. The extent of the mass and nodal involvement following a positive biopsy is proba-

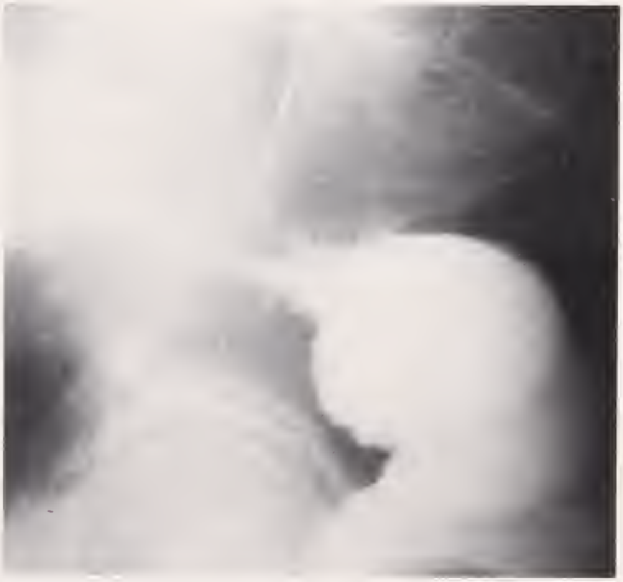

FIG. 13. Same case as Fig. 8. Typical "apple core" lesion on Barium enema, lateral rectum film.

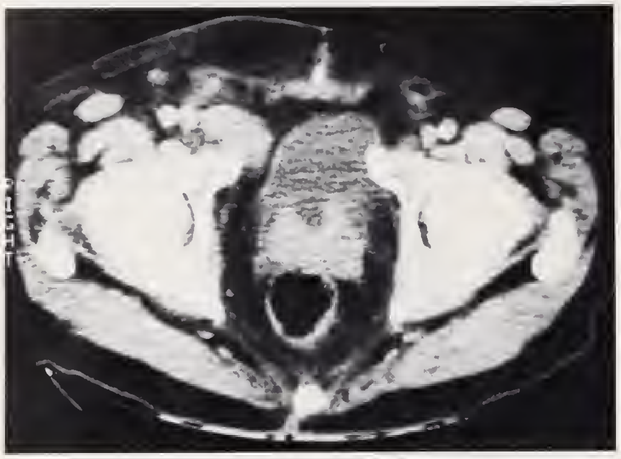

FIG. 14. CA Prostate– Gland is enlarged and is indenting the urine within the bladder without evidence of bladder wall thickening. Benign prostatic hypertrophy may look identical but would not account for the large lymph node seen in the right inguinal area.

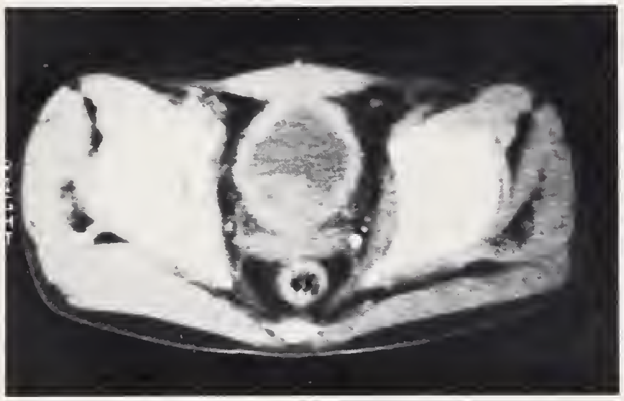

FIG. 15. CA Bladder is represented by a mass in the posterior portion of the bladder and marked bladder wall thickening in all areas. There is no evidence of nodal metastases. Note normal seminal vesicles.

bly best examined by computerized tomography rather than lymphangiography (7). The limitations of both modalities are that the microarchitecture of the lymph nodes is not evaluated so that early metastatic disease may be missed. CT does have the advantage of easily visualizing seminal vesicles and enlargement of these structures or fusion of the angle of the seminal vesicles with the bladder are early indications of prostatic metastases beyond the capsule of the prostate gland (Fig. 14) (3).

Bladder Carcinoma may be visualized at CT as polypoid, fungating masses or thickened urinary bladder wall (Fig. 15). The differential diagnosis of cystitis is not possible without clinical or biopsy collaboration. Metastatic lymph node disease is relatively easy to visualize by means of CT as well as other benign complications such as bladder stones or diverticula.

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Transjugular Approach to Carotid Cavernous Fistulas

Alex Berenstein, M.D. and Claude Manelfe, M.D.

The treatment of carotid cavernous fistulas by a transvascular approach has been well established. Using a variety of techniques, two major routes have been used. The first by the arterial side with the use of muscle (1), balloon tipped catheters (2), and, more recently, with detachable balloons that may preserve the arterial flow (3, 4). The second approach, by the venous side, is performed either by direct surgical attack (5) or by the use of thrombogenic techniques (6). Mullan has demonstrated the possibility of using a balloon tipped catheter for the occlusion of fistulas in which the communication is towards the posterior-superior compartment of the cavernous sinus. We report our experience in one case in which this approach was used successfully.

Case Report

A 25-year-old male was first seen in 1973 after a motor vehicle accident. He was in coma for nine days, after which a right 6th nerve palsy associated with an intracranial bruit was noted. A blow out fracture of the orbital floor was present. After surgical intervention for the orbital floor fracture in June 1974, the right 6th nerve palsy and bruit persisted. A right pulsatile exophthalmos developed. The patient was re-operated in October 1974 for the persistent 6th nerve palsy and the exophthalmos; a prominent vasculature was noted. An orbital venogram was performed that failed to demonstrate the ophthalmic venous system. The exophthalmos had periods of fluctuation and eventually resolved spontaneously. The diplopia and bruit persisted. In June 1979, he was referred to C.H.U. Hospital in Toulouse, France.

At admission, a right 6th nerve palsy and a loud intracranial bruit was present. Angiographic investigation revealed a high flow, right carotid cavernous fistula with drainage to the posterior-superior compartment of the right cavernous sinus-inferior petrosal sinus and internal jugular vein (Fig. 1). Under general anesthesia and with the head turned 45° to the contralateral side, percutaneous catheterization of the right internal jugular vein was performed. After progressive dilatation, a 7F thin wall polyethylane catheter was selectively placed at the inferior petrosal-internal jugular confluence. A pressure contrast injection filled the internal carotid artery and intracerebral vessels in a retrograde fashion (Fig. 2). A 3F Fogarty catheter was then introduced in coaxial manner and placed in the posterior-superior compartment of the right cavernous sinus (Fig. 3). Repeated attempts to inflate the balloon at the narrow segment of the fistula were unsuccessful. Balloon inflation would displace the catheter to the more posterior and dilated segment of the cavernous sinus (Fig. 4). An immediate control right internal carotid angiogram demonstrated some leakage of contrast material through the fistula and stasis in the late phase (Fig. 5). The balloon was left inflated in that position. A repeat internal carotid angiogram 25 minutes later showed further thrombosis (Fig. 6). The catheter assembly system was left in place; both catheters were bent, clipped, and cut at the puncture site. A control right internal carotid angiogram after five days demonstrated complete occlusion of the fistula, with an aneurysmal dilatation at the site of repair (Fig. 7). A jugular venogram showed patency of the internal jugular vein and sigmoid sinus, but occlusion of the inferior petrosal sinus. The 7F catheter was recovered and the Fogarty catheter was buried under the skin. A follow up angiogram three months after repair showed further shrinkage of the aneurysmal pouch (Fig. 8). Clinically, the bruit disappeared after the repair; the 6th nerve palsy has been unchanged. The balloon has deflated.

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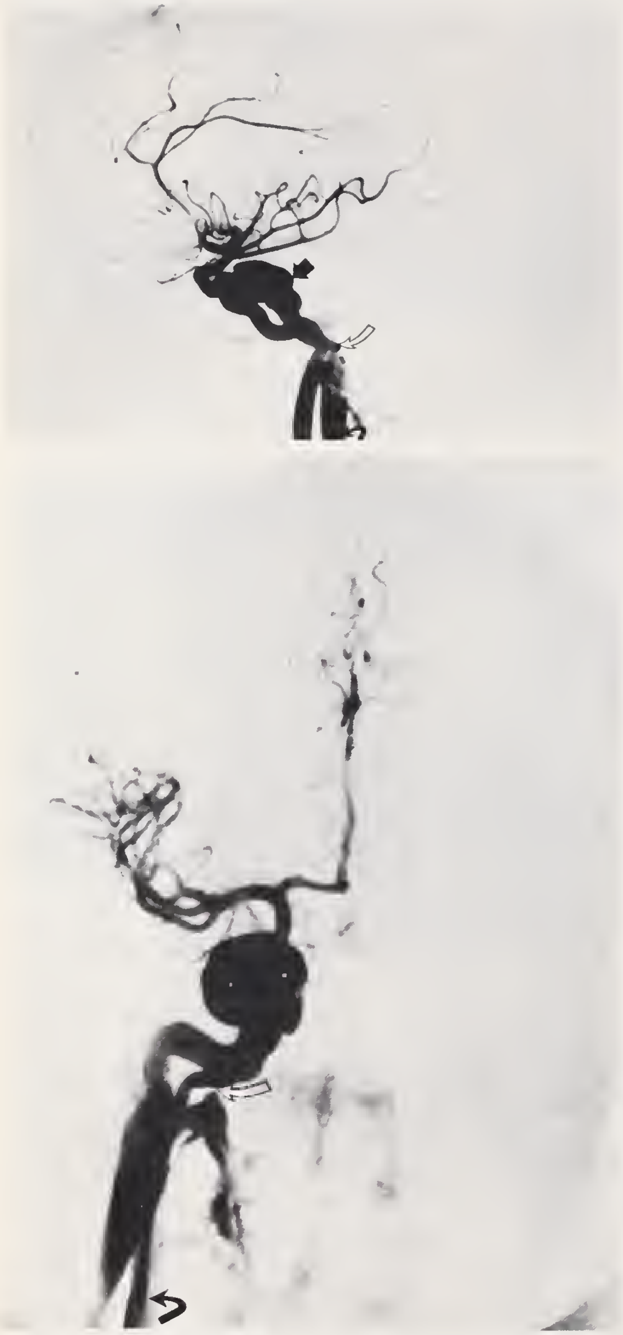

FIG. 1. A) Lateral and B) Frontal subtraction angiogram of the right internal carotid artery draining to the posterior superior compartment of the right cavernous sinus (arrow), inferior petrosal sinus (open arrow) and internal jugular vein (curved arrow).

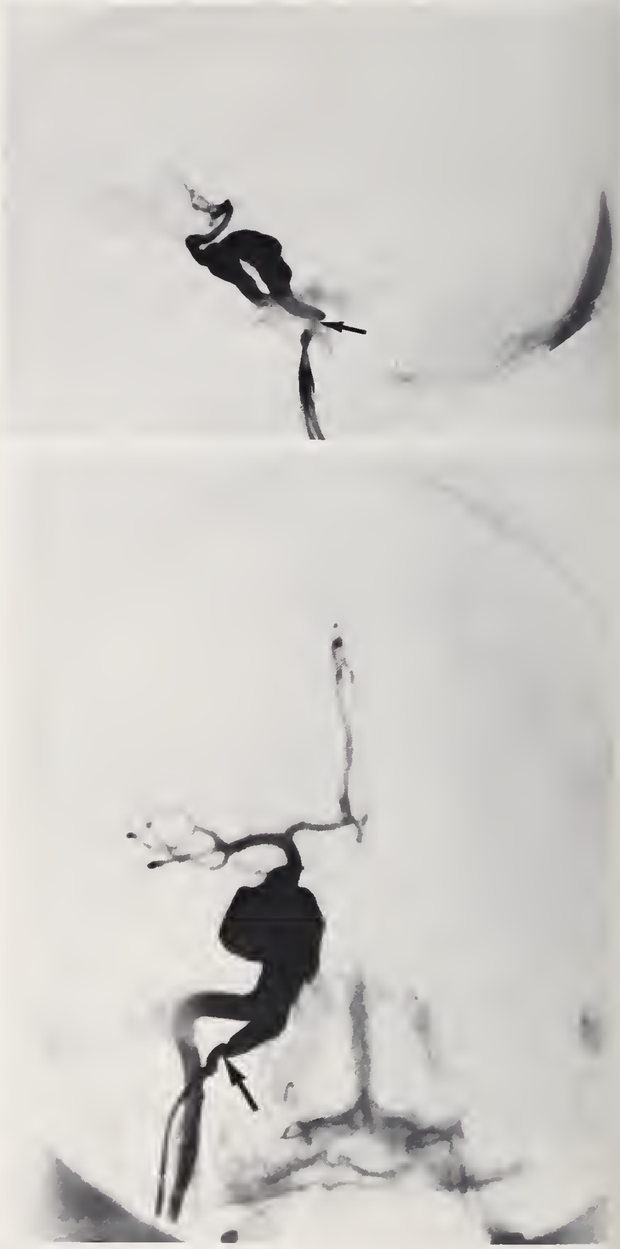

FIG. 2. A) Lateral and B) Frontal subtraction venogram with the catheter tip at the internal jugular-inferior petrosal junction (arrow). Note retrograde filling of the right internal carotid and intracranial branches.

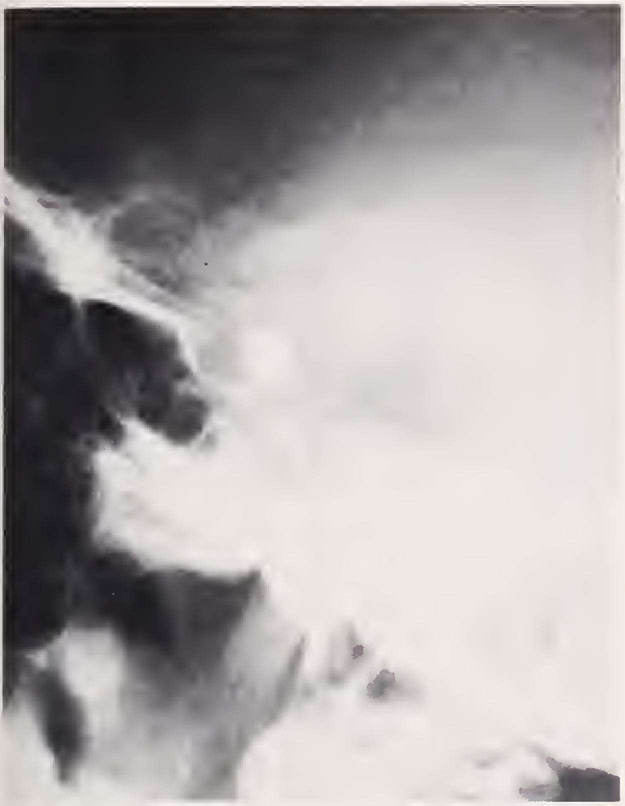

FIG. 3. Lateral skull x-ray shows the inflated balloon in the cavernous sinus.

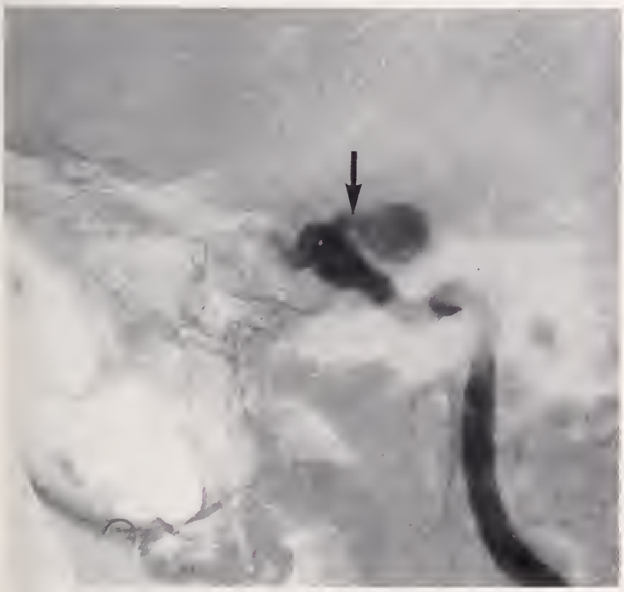

FIG. 4. Lateral subtraction angiogram in early arterial phase demonstrates the narrow fistula communication (arrow).

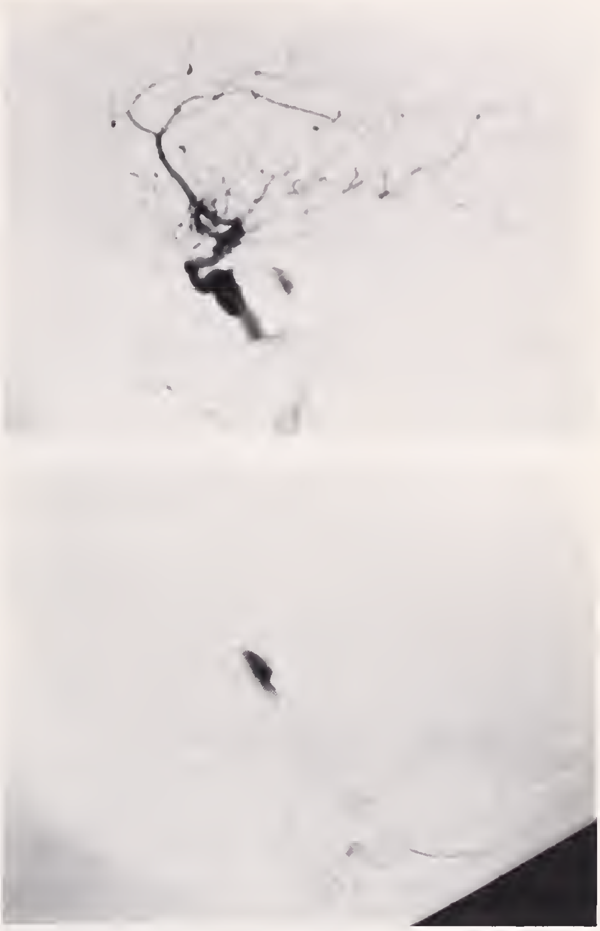

FIG. 5. Lateral subtraction angiogram of the right common carotid artery immediately after balloon positioning. A) early and B) late phase, note leakage of contrast material around the balloon and stasis in the late phase.

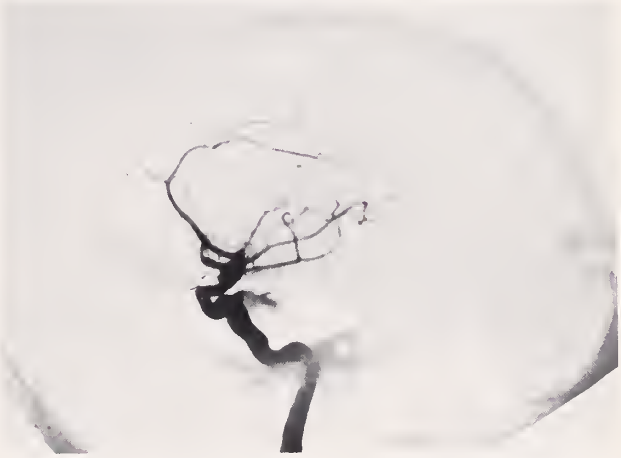

FIG. 6. 25 minutes later, there is further thrombosis.

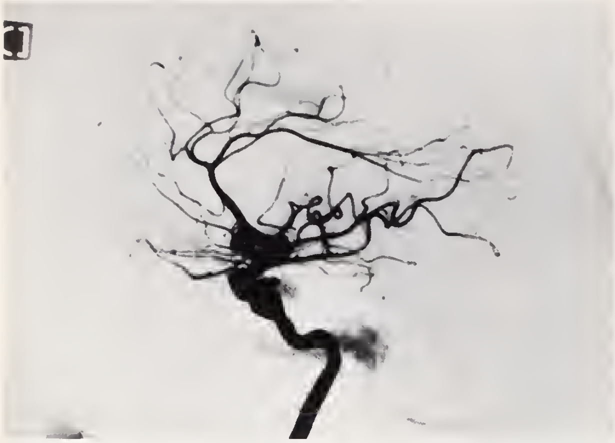

Fig. 7. Five days later there is complete thrombosis of the fistula; the balloon is still inflated. An aneurysmal dilatation of the internal carotid artery at the site of repair is noted.

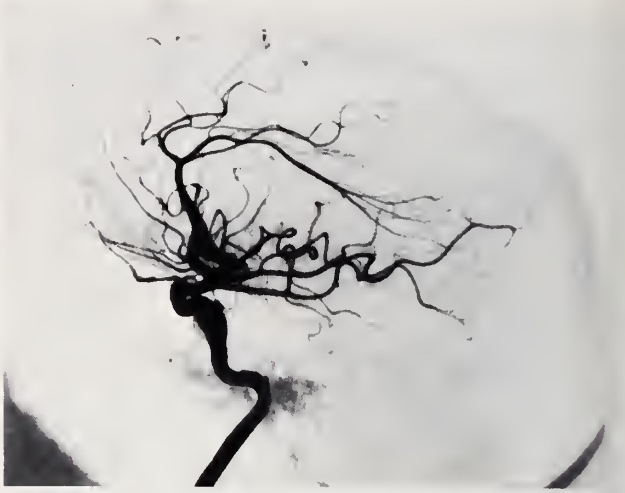

Fig. 8. Control angiogram of right internal carotid artery three months later, the balloon has completely deflated and the aneurysmal dilatation has reduced in size.

Discussion

The transjugular approach to carotid cavernous fistulas is the ideal treatment for fistulas with the proper anatomic arrangement (to the posterior-superior compartment and draining into the inferior petrosal sinus jugular confluence). It has the main advantage of a percutaneous approach, the safeness of a venous manipulation without the risk of cerebral embolization, and the possibility to preserve the carotid flow. Unfortunately, this type of anatomic arrangement is uncommon in this disease. Mullan has attempted this technique in four cases, but was able to reach the lesion in only one occasion with occlusion of the fistula. In his successful case, he had to deflate and remove the balloon after five days because of trigeminal pain (6). We have attempted this approach on two occasions. In the first, we were unable to catheterize the inferior petrosal sinus and had to use the arterial side to repair the fistula (7). In the second case, we experienced no difficulty in catheterization of the inferior petrosal sinus or repair of the fistula.

Based on this very limited experience, but in view of the safeness of this approach in repairing the fistula and preserving the carotid flow, when this anatomic arrangement is encountered, we conclude that an attempt for these procedures should be first in the treatment of the fistulas. Optimal angiographic investigation (8) may aid in selecting suitable candidates in a specific lesion.

Summary

The repair of a carotid cavernous fistula via the jugular-inferior petrosal cavernous sinus route is reported. The safeness and effectiveness of this approach makes this technique the treatment of choice when the fistula drains to the posterior-superior compartment of the cavernous sinus and into the internal jugular vein.

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The Place of the Anesthesiologist in the Department of Radiology

DAVID C. C. STARK, M.D.

It is indeed an honor to contribute to this special edition of the Mount Sinai Journal of Medicine in memory of the late Dr. Bernard Wolf. Although our professional paths crossed but rarely, I greatly admired him and take pleasure in commemorating his contributions to radiology and his dedication to excellence in The Mount Sinai Medical Center.

The participation of an anesthesiologist in a department of radiodiagnosis varies considerably from hospital to hospital and from country to country. There are situations in which the services of an anesthesiologist are not even available, much less obtainable, on request.

When analgesia and sedation are required, they are commonly ordered on the ward and administered to the patient prior to his arrival in the department. The results of this practice may be less than optimal. In such circumstances, the radiologist functions both as operator and anesthesiologist, a situation that could be a malpractice hazard and could cause an undue strain upon the operator. Before elaborating on the multiple functions performed by an anesthesiologist in the Department of Radiology, a few words on the Radiology Department would be appropriate.

In past days of explosive anesthetic agents, it was required that flammable agents be used in underventilated areas, without conducting floors, and in rooms containing high voltage electrical equipment, transformers, circuit breakers, etc.

The floors were nonconductive to protect the staff from the risk of electrocution. The absence of conducting floors made little difference to the hazard of static electricity—such a nuisance in dry operating conditions—when flammable agents were used and could be ignited by a static spark. The ionizing effect of, even short, exposures in an x-ray room make it impossible for meaningful static charges to develop. However, the risk of explosion, due to electrical problems remained, and advice was always given to use ether and air (as opposed to ether oxygen-nitrous oxide mixtures) because ether and air were less likely to ignite!

Now that most leading institutions in the world have abandoned explosive anesthetics, this has become less of a problem but a new dimension has complicated the provision of safe conditions for the administration of anesthesia.

The effects of chronic pollution by trace amounts of anesthetic agents, in the ambient air, have become very much an engineering problem and the constraints laid down by the Occupational Safety and Health Administration have created considerable problems.

The recommendations of various regulatory agencies have defined x-ray facilities in which invasive procedures are performed as "procedure rooms" and recommend a degree of ventilation predicated only upon the comfort of the personnel engaged in these areas. Such ventilatory requirements vary from about one to eight changes of air per hour.

To meet the OSHA standards, pollution can only be avoided by bringing the ventilatory conditions up to a standard approaching that of an operating room, that is, about 20 changes of air per hour. In addition, careful scavenging of the anesthetic apparatus and particular care on the part of the anesthesiologist should be maintained to avoid accidental or incidental pollution of the atmosphere.

Additionally, it is essential that hospital administrators, architects, and engineers provide the x-ray department, in the procedure rooms where general anesthesia might be required, with exactly the same provision for services that could reasonably be expected in an operating room. Piped oxygen, nitrous oxide and line suction should be in any room where anesthesia is to be administered. Because of the increased sophistication of modern diagnostic machinery and the tendency for procedure rooms to be closely dedicated to one particular type of procedure, this represents a considerable construction expense.

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Some argue that the use of tanks of appropriate gas on the anesthetic machine could be satisfactory; however the length of procedure and the oxygen consumption of many ventilators might invite hypoxia should this system be used.

This is particularly true in institutions in which the entire anesthetic department is accustomed to the luxury of piped gases and is not familiar with the problem of working with small tanks.

Line suction, safely vented to the outside atmosphere, is necessary when scavenging devices are in use. Portable, electrically operated, suction units do not satisfy this requirement. Also, adequate power outlets should be provided for whatever electrical equipment, EKG monitor, ventilator, etc, the anesthesiologist might require.

Procedure rooms, in the blueprint stage, appear to be large and capacious until the x-ray equipment is designed, chosen, positioned and orientated for the benefit of the radiologist. This is entirely his prerogative, but it has the effect of displacing the anesthesiologist and his equipment into the most remote, inconvenient corner of the area.

While in the past this may have been tolerated, the regulatory agencies now require that an anesthetic administered in any area of a hospital must be administered according to the overall institutional guidelines. It is the duty of the Director of Anesthesiology to advise the institution's Medical Board to establish prerequisites for the administration of anesthesia that apply uniformly throughout the institution. There can be no reduction in standards governing the safety regulations for the administration of anesthesia merely because the anesthetic is administered outside the operating room suite.

For example, quality safety conditions are particularly pertinent when emergency invasive contrast radiography is undertaken immediately prior to lifesaving surgery. No anesthesiologist dare induce anesthesia in an emergency situation on anything other than an operating table that can be instantly tilted into a head-down position should vomiting or regurgitation of gastric contents occur prior to tracheal intubation. Yet few x-ray tables are capable of being put into lifesaving position with the necessary speed and safety.

Another problem in the design of x-ray procedure rooms is that many rooms have become so overspecialized, the anesthesiologist is often expected to move his anesthetized patient from one room to another. This happens following a CAT scan when there is a need to complete the examination by performing carotid angiography. It always seems to happen that the serial changer necessary for carotid angiography is diametrically opposed to the CAT scanner.

Additionally, when examination of the urogenital system is required, it is impossible to obtain an incidental chest x-ray without having to move the patient to another table in another area of the department.

Once, after a CAT had been installed in the hospital, I received a note from the x-ray department Administrator demanding the provision of two 30-foot lengths of pressure tubing so that the oxygen and nitrous-oxide outlets could be connected to the anesthesia machine. These outlets had actually been placed in an area where they were completely inaccessible to the anesthesiologist during performance of the scan.

Thus, better, more inclusive planning of procedure room design will promote patient and staff safety and ensure that the anesthesiologist makes an effective contribution to the production of the highest quality diagnostic films; in short, quality patient care.

CLINICALLY, THE ROLE OF THE ANESTHESIOLOGIST IS: 1) to provide general anesthesia for invasive contrast radiology; 2) to assist the radiologist in obtaining the highest of quality films, by his ability to manipulate the patient's homeostatic mechanisms; 3) to render the assistance in resuscitation of the unfortunate patient who has an adverse reaction to a procedure, and/or more importantly to help avoid such a reaction by monitoring vital signs, attending to the adequacy of respiration, cardiac output, and body temperature; 4) to assist in resuscitation should all these measures fail; and, 5) to participate in staff education in cardiopulmonary resuscitation.

Indications for the Administration of General Anesthesia for Invasive Contrast Procedures

The need for general anesthesia has varied over the years. Twenty-five years ago, when x-ray equipment was not as sophisticated as it is today, the exposure time, the lack of serial changers, the slow film, and the manual development of the negatives predicated that the patient be absolutely still during exposure. Respiration was held in abeyance by the administration of a muscle relaxant and that required a state of general anesthesia.

In certain circumstances, for instance in cerebral angiography, the approach to the cerebral circulation was via a percutaneous carotid puncture which was painful, required a still patient, and a reasonably high blood pressure for easy palpation and entry of the vessel. By contrast, in the latter half of the century, the Seldinger approach to the cerebral vessels remotely, through a catheter that can be positioned under fluoroscopy, has proved to be less traumatic for the patient and has obviated the need for a completely still patient. In addition, the rapidity with which serial exposure can be made has made slight movement of the patient less catastrophic to the goal of obtaining high quality diagnostic films.

The ability to dilate or constrict the cerebral vessels according to whether the patient was maintained in a hypercarbic or a hypocarbic state is of importance. Altering the caliber of the cerebral vessels on demand can result in more useful films and, therefore, a greater diagnostic accuracy. This is particularly true with respect to the assessment of cerebral spasm resulting from subarachnoid hemorrhage, the visualization of cerebral aneurysms, and arteriovenous malformations.

While it is entirely possible that the combination of computerized axial tomography and regular contrast cerebral angiography has transcended this need, it is important that both the anesthesiologist and the radiologist be aware that the particular acid base conditions under which a particular set of films was obtained can have a major bearing upon their interpretation.

In the field of neuroradiologic diagnosis, the procedure of pneumoencephalography demands attention. As is well known, this procedure involves lumbar puncture, removal of a considerable amount of cerebrospinal fluid, and the injection of a comparable amount of air to function as a contrast medium. This involves sitting the patient up, performing lumbar puncture, injecting the air and then maneuvering the patient into multiple positions to persuade the air to enter the appropriate compartment of the ventricular system. This is the most unpleasant procedure ever inflicted upon a conscious patient. Nevertheless, the information provided has been vital to diagnosis and subsequent surgery. Management without anesthesia in the adult can be traumatic but there is little alternative because of the number of different positions that have to be adopted during the exposure. However, in the child, who really must be anesthetized, it represents one of the most difficult anesthetic procedures required of an anesthesiologist. For example, small infants with hydrocephalus have difficult airways and the positions required for the x-ray involve the risk of considerable compromise of these airways, even if they appear to be guaranteed by an endotracheal tube.

A further complication is injection of air. It persists in ventricular system for some time, quite often into the operative period. The administration of nitrous oxide during such an anesthetic results in an increase in intracranial pressure following diffusion of nitrous oxide from the blood into the air-containing space—a trap for the unwary anesthesiologist.

Such is the problem of raised intracranial pressure following this procedure, that some recommend the use of nitrous oxide as a contrast gas. CAT scanning has almost totally replaced pneumoencephalography.

In other areas of neurosurgery, the need to perform myelography under anesthesia has lessened drastically, again as a result of the amazing accuracy of CAT scanning. Prior to the development of this magnificent computer, it was often required that a small child stand several hours in the dark during fluoroscopy, under combination of sedation and/or anesthesia, being tipped into various positions, at considerable risk to the airway of the patient and to the detriment of the cervical spine of the anesthesiologist. A good description, if somewhat historical, is to be found in the article by Whitby (Anesthesia 1960).

Although CAT scanning has transcended many invasive procedures that previously needed anesthesia, there still remain situations in which formal anesthesia is required—even for CAT scanning. Organic mental syndrome, Parkinson's disease, subdural hematoma, and brain-damaged children are all conditions in which the patient cannot be adequately cooperative or mildly restrained so that accurate pictures can be obtained.

Because of the nature of the apparatus, the patient's airway becomes increasingly inaccessible to the anesthesiologist, who must be outside the procedure room during the x-ray exposures. The safe solution to such a situation is to administer a formal endotracheal general anesthetic, correctly monitored by continuous EKG, and remote recording other vital signs. This can be a relatively simple procedure in the nonemergent case. However, when x-rays are required in the diagnosis of acute closed injuries of the brain in an uncooperative patient, it should be remembered that many anesthetics, particularly halothane, can interfere with regional blood flow to the extent that a damaged area, marginally supplied, could be rendered totally ischemic by the anesthetic. It is probably wiser to avoid the use of volatile anesthetic agents in such circumstances lest they further compromise an already dangerous situation.

Turning our attention to the respiratory tract, one of the most exacting procedures that was ever required of an anesthesiologist was to anesthetize a small child for bronchography. Bronchiectasis, for which bronchography was the most common indication, has become an increasingly rare condition but bronchograms are occasionally still required.

One procedure was known as the "drowning technique." This consisted of anesthetizing the child with open ether to a relatively deep plane of surgical anesthesia, pouring contrast medium into the oropharnyx, holding the child's nose and mouth to assure that the child, thus obstructed, would aspirate the contrast medium from the pharynx into the bronchi and thereby outline them!

As can be imagined this was somewhat drastic procedure and was superseded by more meticulous techniques that involved normal anesthesia of the child, endotracheal intubation, and instillation of the contrast medium via the endotracheal tube. Often, this procedure was preceded by bronchoscopic toilet. In the anesthetic literature, there is considerable discussion as to whether the child should breathe spontaneously or be apneic during the exposure of the x-ray films. There were those who claimed that exposure during spontaneous respiration gave a more dynamic assessment of the bronchial musculature and a better anatomic demonstration of the tracheobronchial tree.

The contrary argument was that it was safer for the child to be ventilated during this procedure, although such a technique could be accompanied by a considerable amount of "alveolar fill." This could obscure bronchial anatomy, yet if alveolar fill occurred, the possibility that bronchiectasis existed was almost excluded since peripheral filling was possible. When a department handled many child and adolescent bronchograms, it was important that the anesthesiologist and the radiologist mutually discuss pharmacologic implications and the anesthetic administered, so that there would be uniform interpretation of the films.

If ether were used for bronchography, the caliber of the bronchi was considerably greater than that seen with an anesthetic technique, that did not alter the caliber of the bronchi or even constrict them, was used. This was also of importance for a comparison of films made in different institutions.

The modern technique of aerosoling contrast medium into the respiratory tract by using a nebulizer has to be a certain extent eliminated the need for anesthesia in such children and constitutes an advance in the safety of this examination.

Cardiac Catheterization

The information obtained by cardiac catheterization and angiocardiography is considerable and needs no justification. However, the developmental history of this procedure is noteworthy. In the early days, only right heart catheterization was feasible and the determination of intracardiac shunting could only be made by blood gas analysis. The only available technique was the Van Slyke method which precluded the use of nitrous oxide. In addition, the administration of an inspired concentration of oxygen greater than that of air invalidated the test results. It was essential that such patients be managed with a combination of sedation and respiration with ambient air. This commonly involved the use of rectal thiopental and, if necessary, supplementation by intravenous doses of the same drug.

It was not then appreciated exactly how depressant the barbiturate molecule was on the function of the myocardium. Surely many shunts were overestimated by the failure to distinguish between the gradient observed, the diminished cardiac output, and that due to pure shunt. On occasion, the net result of a prolonged examination was reversal of a left to right shunt, and several hours of great concern until the barbiturate was excreted and nature restored the situation. In contrast, today blood gas analysis can be accurately obtained in a matter of minutes and not be compromised by any anesthetic agent that the anesthetist cares to administer. Because of the easy access to the left side of the circulation, shunts can be determined and photographed by various cine-radiographic and serial changer techniques which can prove the existence or absence of shunts and quantitate them accurately.

Indeed, the emphasis on blood gas analysis during cardiac catheterization has changed considerably and it is now used less as a diagnostic tool to determine the nature of the congenital abnormality and more as a means to assess the state of the infant during examination.

In this context, the pressure volume relationships determined during cardiac surgery bore very little relationship to those measured during cardiac catheterization. It must be fully appreciated, when interpreting such measurements, what the anesthetic administered at that time actually was and whether the patient was breathing spontaneously or being ventilated.

The management of such children should be determined by joint discussion well in advance of the actual procedure. The most common mode of handling such patients these days is the administration of intramuscular ketamine supplemented by small aliquots of the same drug intravenously. The reason for the choice of this agent is that it is the only agent which, in legal dosage given intramuscularly, will produce a state of surgical anesthesia. It is credited with maintaining left heart function, increasing the cardiac output and the total peripheral resistance. This will have the protective effect of avoiding shunt reversal caused by sudden reduction of after load.

This is extremely important when a child could be intolerant of shunt reversal. However, there are situations when this additional stress on the left side of the heart may be tolerated. Although the catheterization is being undertaken to define the lesion anatomically, it should be established in advance what particular condition is likely to be present.

As for adults, the sheer volume of patients being subjected to angiography precludes attendance of the anesthesia department. Yet it is a moot point whether a patient suffering from angina, a condition notoriously susceptible to the hormonal effects of anxiety, should be subjected to such a procedure without the benefits of an anesthesiologist and intravenous sedation. If such minute-to-minute control of the situation cannot be organized, it is required that the cardiologist and staff be cognizant of the needs of cardiopulmonary resuscitation, and that the particular precedure room be adequately equipped to handle both cardiac and respiratory emergency.

Again, it should be noted that the particular configuration of the x-ray table—nay trough—which is used, can make resuscitation extremely difficult by denying adequate anatomic access to the airway.

The angiocardiographic procedure room should be close to the cardiac operating suite so that patients suffering from pulmonary embolization, incipient infarction, postinfarction ventricular septal defect, or complications of cardiac catheterization can be moved rapidly to the operating room on the discovery of a surgically correctable, life threatening lesion.

Hormone Secreting Tumors

When contrast radiography is required, the various hormone secreting tumors require sophisticated monitoring, if not actual anesthesia. Over the years, the diagnosis of pheochromocytoma has become less exacting. Prior to the availability of the wide range of alpha and beta blocking drugs that we now have, such patients were subjected to various procedures, for example, intravenous pyelogram, presacral insufflation of air to locate a catecholamine secreting tumor, and were at risk to grave hypertensive crises. Now that more selective angiography is available, combined with differential venous sampling, the localization of such tumors has become very much more accurate and there has been less excitement in the x-ray departments when such patients come for examination. Nevertheless, the stress of the examinations and invasiveness of the procedures still require that patients be monitored with intraarterial lines and that blood pressure be controlled by appropriate administration of alpha blocking agents.

Other hormone secreting tumors are of interest to the anesthesiologist. For example, the apudinomas have become more readily diagnosable and more amenable to treatment. These tumors, arising usually in the distal small bowel secrete serotonin, are normally destroyed in the liver. When liver metastases occur, this hormone is released into the circulation, resulting in attacks of flushing, abdominal cramps, severe bronchospasm, and unpredictable variations in blood pressure. The modern approach to the management of these conditions is to embolize the branch of the hepatic arteries supplying the area of the liver containing the greatest density of secreting metastases in an effort to reduce hormonal output. This procedure commonly precedes resection of the appropriate lobe of the liver.

Even if the procedure can be performed without the induction of actual anesthesia, careful monitoring of such a patient demands, at the very least, an intraarterial line and, occasionally, Swan-Ganz catheterization to assess the pulmonary artery pressures. It can be extremely difficult to distinguish between low and high cardiac output syndromes. Minute-to-minute control of the patient's circulation is of paramount importance to his survival.

The information obtained during the conduct of anesthesia for invasive radiologic procedures is of great importance when subsequent major surgery is to be undertaken. This is particularly true in the management of patients suffering from Serotonin secreting tumors. It has been the experience of our department that the anesthesiologist who negotiates the patient through the embolization should be the physician concerned in the conduct of the more major operation.

The Urologic System

A common demand upon the anesthesia department is to provide anesthesia for cystologic diagnosis at various ages. The neonate with a major malformation of the urinary tract needs both the urologist and the anesthesiologist. Such congenital defects can be life threatening and the sheer size of the tracts and orifices to be examined strain the optical instruments. In addition, the metabolic state of the infant renders it extremely liable to the complex problems of hypoglycemia, hypothermia, and electrolyte imbalance. The principal problem facing the anesthesiologist is the maintenance of body temperature and the application of external heat, commonly supplied by thermal blankets which, in turn, complicates the exposure of x-ray pictures.

In the slightly older age group, the condition that used to be labeled recurrent pyelitis is now recognized to be incompetence at the uteretrovesical junction. What is commonly described as a "pediatric workup" involves a voiding cystogram, a cystoscopy, an IVP and, not uncommonly, urethral calibration. These examinations are commonly performed on ambulatory patients. For a useful voiding cystogram to be obtained, it is necessary that the child receive no premedication, be induced by an inhalation anesthetic, and be awakened so that micturition can take place spontaneously. If the child is premedicated, particularly if he receives atropine and undergoes an intervenous induction, it can be extremely difficult to obtain films during spontaneous micturition. While there may be some doubt as to whether spontaneity is absolutely essential, many urologists believe that external abdominal pressure can artificially produce reflux in the lower ureter and lead to a misdiagnosis.

A good deal more can be done in the female child without the use of anesthesia but it is extremely difficult to handle a small male child for such an examination without the administration of general anesthesia. A great deal of patience and personality is required to handle nonmedicated small patients, if they are not to be unduly psychologically traumatized by their experience.

In older age groups, the services of the anesthetist in the x-ray department revolves mainly around retrograde pyelography and "basketing" of lower ureteric stones. Many patients with stones impacted in the lower ureter can be spared open operation if the radiology facilities are equipped for instrumentation of the lower ureter under fluorscopic control and adequate anesthesia. It is true that spinal or epidural anesthetic is an eminently suitable choice, provided that the patient is agreeable and anatomically suitable for this type of anesthesia and that it can be safely administered. It is now reaching a point at which it is not quite clear whether an operative procedure is being performed in the radiologic suite or whether a radiologic procedure is being performed in the operating room.

This reiterates the thoughts stated earlier in this article about the adequate provision of the necessary facilities and ambient atmosphere so that patient and staff may be protected from various physical hazards.

Vascular Surgery

In past years, it was required that patients undergoing translumbar aortography be paralyzed and therefore anesthetised during the injection of the contrast medium and exposure of the films. Technologic advances have made it unnecessary for the respiration to be held in abeyance during such procedures and, as mentioned earlier, Seldinger techniques and their variations have made peripheral angiography extremely safe.

As new techniques develop, demands may very well be made on anesthesiologists, during the procedure of coronary angioplasty, of percutaneous cannulation of hepatic ducts for endoscopic removal of residual gallstones and potentially many other similar procedures which will obviate the need for surgery. One of the greatest advances in surgery over the past fifteen years has been in the development of fiber optic illumination, fiber optic instruments, and operating microscopes. Over the same time period, vast developments in the technology of contrast radiography have matched the advances in surgical optics to the extent that we have reached the point or, almost reached the point, at which John Hunter started—he being known as the Reluctant Surgeon.

It would be appropriate to include a few words about the management of the allergic patient. A very common request for an anesthesiologist to attend in radiology stems from the need to inject contrast materials in a patient with an allergic history or a history of adverse reaction to contrast dyes. Allergy to fish is not related to allergy to organic iodine compounds, contrary to common impression. However, there are patients who have had severe reactions to such dyes, who require essential studies.

It is our practice to manage such patients by pretreating them with steroids for 48 hours prior to examination and to combine this with pretreatment with long-acting antihistamine preparation. At the time of examination, an intravenous line is secured, an EKG monitor attached, the blood pressure carefully monitored and resuscitative drugs, particularly hydrocortisone, adrenalin, sodium bicarbonate, pentothal, anectine and facilities for endotracheal intubation are prepared and are instantly available. Adherence to this regimen has been successful as there have been very few problems related to patients with allergic histories. Problems have occurred when the allergic history as either not been elicited or a particular patient has reacted adversely. The patient most likely to react adversely to contrast media injected into the circulation is the obese, hypertensive, bronchitic female. Such a patient commonly presented with hypertensive heart disease. Their physicians, to discover a surgical cause for the hypertension, for example, Goldblatt kidney, had intravenous pyelograms performed. On occasions, these could result in catastrophic anaphylactic shock, a very difficult condition to treat but one which is relatively manageable if adequate precautions are taken beforehand.

The pharmacologic effects of many of the agents used in contrast radiography are quite powerful and, familiarity breeding contempt, are sometimes somewhat ignored. The organic iodine compounds, on which the majority of examinations are based, are now relatively benign. They are of necessity hyperosmolar, have the high potassium content, and do not carry oxygen. Considerable volumes of these drugs are injected in the course of a normal examination and a result is considerable diuresis. Since many x-ray procedures call for the patient to be NPO for several hours, or to be purged or, to have similar studies on two or three consecutive days, the net result can be dehydration and electrolyte imbalance. It has been the experience of many clinical anesthesiologists that for every x-ray series performed, an additional liter of intravenous fluid is required prior to surgery!

Resuscitation

It is axiomatic, that patients who are hospitalized are, by definition, ill and that complications of illness can be expected. The high concentration of severely ill patients in a radiologic suite inevitably results in a disproportionate number of cardiac arrest calls.

This may be due to the nature of the patient's illness, to a complication of the procedure, or to an act of God. However, it has been common experience over the years that a significant proportion of cardiac arrests occur in the x-ray department.

This demands that all personnel, physician, nurse, technician, orderlies, and transporters, be thoroughly familiar with basic life support (CPR) procedures and that all concerned can provide first-aid measures prior to the arrival of more expert specialists.

It goes without saying that all x-ray departments should be equipped with the necessary resuscitative apparatus to guarantee an airway, provide intravenous infusion, defibrilation and external cardiac compression.

Summary

In summary, the indications for general anesthesia for radiologic procedures are

1. Patient insistence
2. Lack of patient cooperation
3. The need to provide complete stillness for a considerable period during complicated exposures
4. The need to monitor a patient closely and obtain information as to how he will react during surgery
5. Extremes of age.
6. To be able to manipulate the patient's hemostatic mechanisms during the procedure to ensure the highest quality of diagnostic films

There are few situations in medicine today, that do not call for team-work. This is true of the interface between diagnostic radiology, anesthesiology and the surgical specialties. Greater diagnostic accuracy can be assured if the quality of films can be improved and if a knowledgeable anesthesiologist can contribute to this laudable goal.

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Radiologic Notes

Claude Bloch, M.D. and Harvey Peck, M.D., Coeditors

The group of cases described in this **Festschrift** is presented in the same format that Dr. Bernard S. Wolf used in the first installment of the Radiologic Notes that he started publishing in this Journal in 1957. The present editors of the Notes took over from Dr. Wolf in 1962. We have tried over the many years to continue his concept of radiologic teaching by the use of proven cases with careful radiologic description of the pertinent findings. A brief discussion of the disease and the differential diagnosis is presented with high-quality x-ray reproductions, together with an up-to-date selected bibliography on the subject for those who are interested in reading further.

Before Dr. Wolf's untimely death, as a manifestation of his great ability and inquisitive mind, he had managed to master the newer disciplines of ultrasonography and CT scanning. With this in mind, and in memory of our great teacher, we are including in this **Festschrift** some interesting cases of CT and ultrasound, as well as cases related to Dr. Wolf's prime subject of interest, the gastrointestinal tract.

Case No. 400

A 13-year-old boy was admitted with acute intense abdominal pains and vomiting. He had been entirely well until three weeks before his hospitalization, when he developed an upper respiratory infection characterized by fever, sore throat, malaise and submandibular adenopathy. He was given antibiotics with good clinical improvement. The boy returned to full normal activities until the morning of his admission, when he noted the sudden onset of sharp colicky abdominal pains and vomiting. He was admitted to the hospital because of the progressive nature of these symptoms.

On admission, temperature was 101°F, WBC 9,500, with a normal differential, ESR and other blood tests were normal. Physical examination revealed an acutely ill patient who had a faint generalized maculopapular rash. There was tenderness and guarding in the epigastrium and subcostal regions. There was no rigidity or rebound. Bowel sounds were hypoactive and the lower ab-

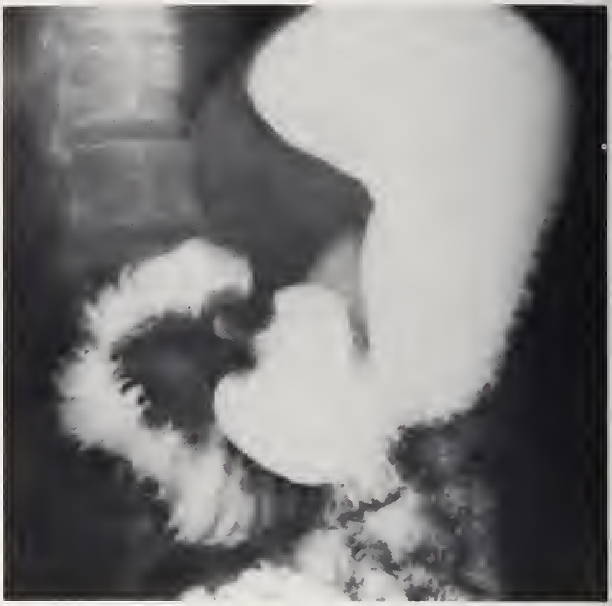

Fig. 1A. Right anterior oblique film of the barium filled stomach and duodenum reveals a segmental involvement of the second and third portions of the duodenum, characterized by an irregular thickening of the duodenal folds. In the area of decreased distensibility in the sweep, the abnormal folds assume a thumbprint appearance, but there is no ulceration.

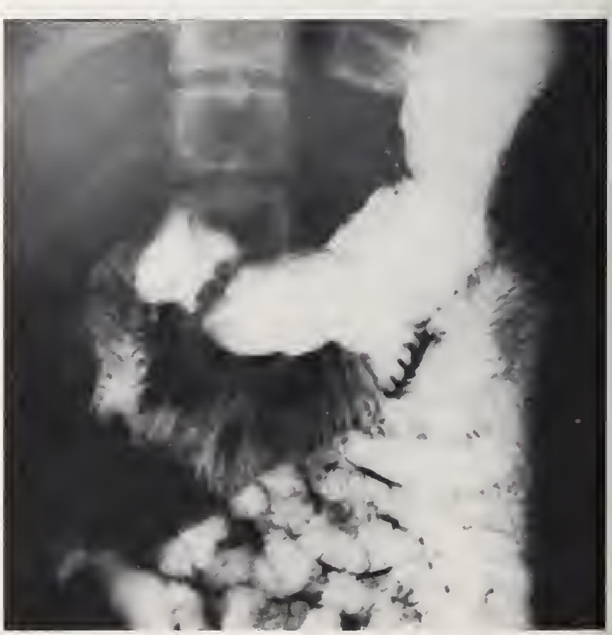

Fig. 1B. Posteroanterior view confirms the above findings. Also note that the fourth portion of the duodenum is slightly distended with thickened folds. The small bowel, distal to the Ligament of Treitz is normal.

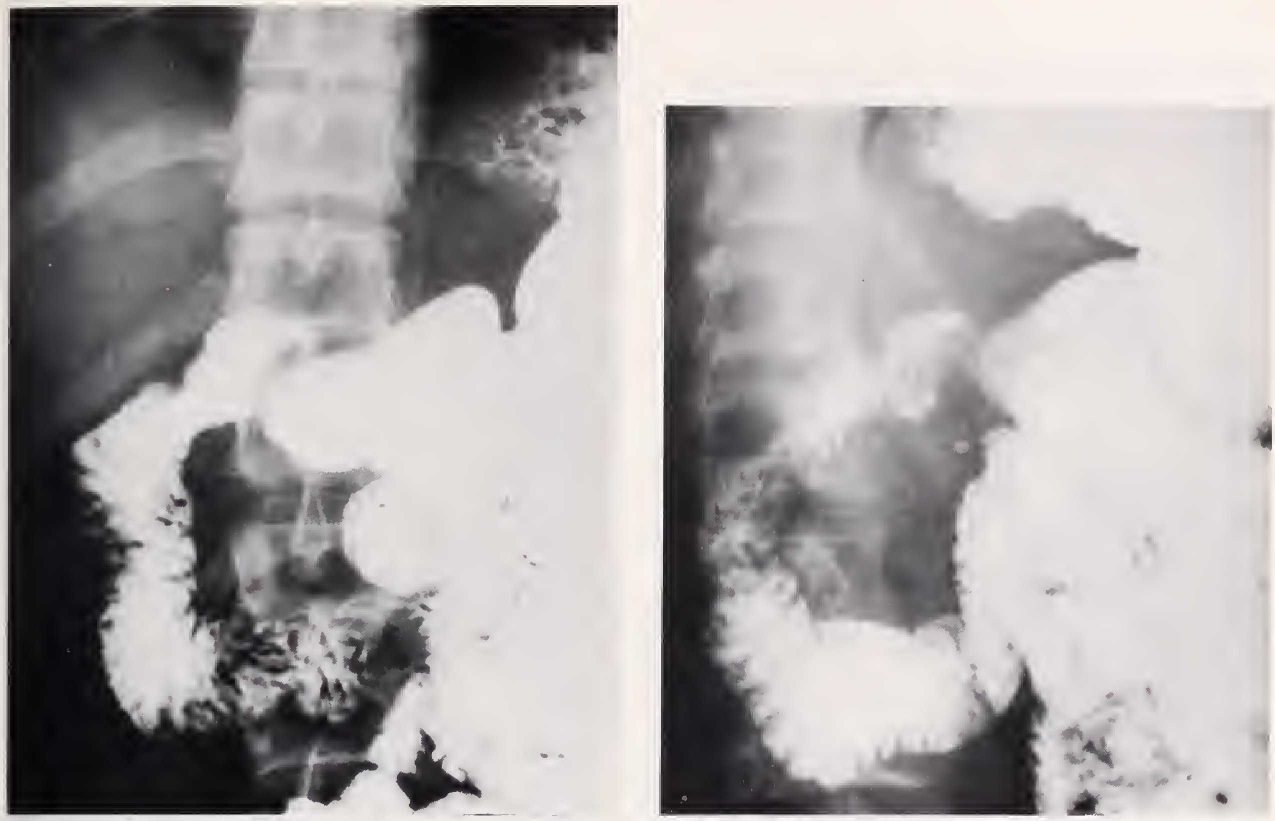

FIG. 2A & B. Thirteen days later the duodenal findings have completely reverted to normal.

dominal regions were relatively normal to palpation. A GI series was performed on the second day of hospitalization. The esophagus, stomach and duodenal bulb were normal. There was evidence of mucosal edema in the duodenal sweep, especially in the descending portion, characterized by irregular thickening of the folds and thumbprinting. There was also decreased distensibility of the affected portions of the duodenum and some irritability of these segments. (Figs. 1A, 1B). After three days of conservative management, the patient's signs and symptoms rapidly disappeared. A repeat GI series performed 13 days after the initial x-rays showed that the duodenal folds and wall distensibility were again completely normal. (Figs. 2A, 2B).

Discussion

See Discussion after Case No. 401.

Case Report: Henoch-Schoenlein's purpura
Case No. 401

Presented by: Judith S. Rose, M.D.

A 7-year-old male was admitted to the hospital because of a flat macular rash on his elbows, knees and buttocks. This rash had been treated by his pediatrician with antihistamines, but it did not improve. Five days after the onset of the rash, he developed severe crampy abdominal pains. Melema occurred two days after admission, and an upper gastrointestinal study, including a small bowel follow-through was performed. The stomach and duodenal bulb were normal. There was slight dilatation and some hypersecretion and mucosal prominence within the second portion of the duodenum. The jejunum and proximal ileum were normal. There was slight narrowing of the lumen of the distal ileal loops in the right lower quadrant and some thickening of the affected bowel, but there was no proximal bowel obstruction (Fig. 1). Supportive and conservative medical management produced complete symptomatic relief. The physical signs in the abdomen disappeared. Repeat gastrointestinal series performed 11 days after the initial study showed a normal duodenum, jejunum and ileum (Fig. 2).

Discussion of Cases 400, 401

Henoch-Schoenlein's purpura can present clinically in many forms. The mildest cases simply show punctate subcutaneous hemorrhages. The

Case No. 401:

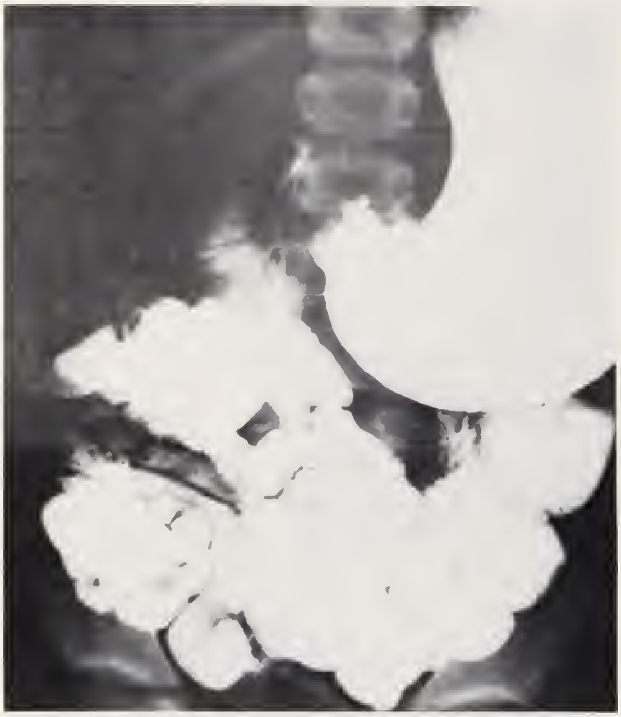

FIG. 1. Posteroanterior view of the stomach and small intestines shows slight dilatation and hypersecretion with mucosal prominence within the second portion of the duodenum. The jejunum and proximal ileum are normal. There is some narrowing of the lumen of the distal ileal loops in the right lower quadrant, with slight thickening of the affected bowel loops.

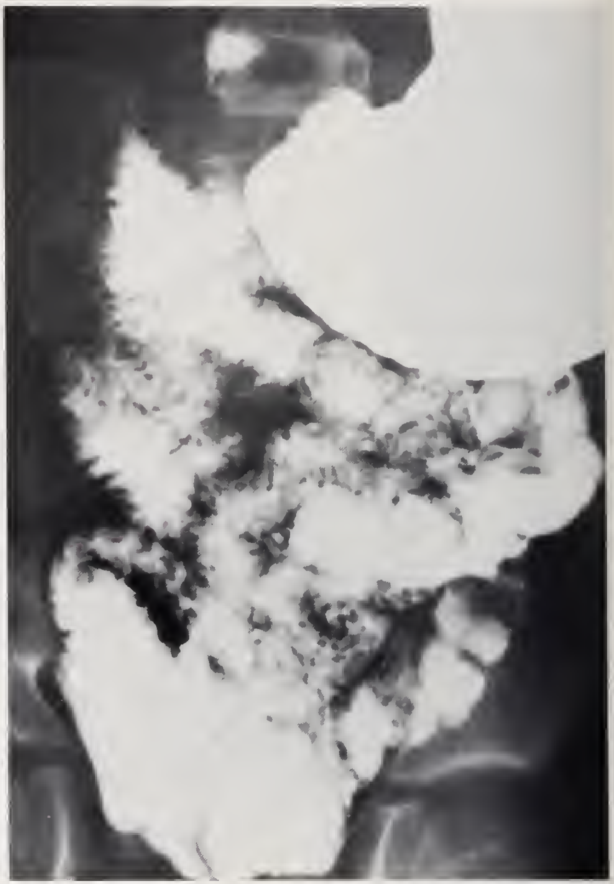

FIG. 2. Repeat study performed eleven days later reveals a normal small bowel.

symptoms can either present insidiously or acutely and, in the more severe cases, there can be intense abdominal pain and other signs of an acute abdomen. There can be intestinal hemorrhage, together with joint pains, purpura, urticaria, proteinuria and acute nephritis and angioneurotic edema. Usually, however, the disease is self limited with the signs and symptoms reverting to normal with supportive therapy and in some cases steroids. Radiologically, there is submucosal edema with thickened and blunted folds which, when severely affected, can present as scalloping and thumb-printing. There may be some degree of bowel dilatation, but no real obstructive features. At operation, the bowel appears reddened and edematous, with preservation of good pulsation. Histologically, there is an acute arteritis with edema and hemorrhage into the mucosa and submucosa. Radiologically, the findings are usually completely reversible as well, and fibrosis does not ensue. Other x-ray findings include intussusception, mostly ileo-ileal, spontaneous bowel perforation, or signs of right lower quadrant inflammation similar to those found in appendicitis.

Case Report: Henoch-Schoenlein's purpura

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Case No. 402

A 59-year-old man, who had been in previously good health, sought medical advice because of malaise, fatigue, and weight loss present for the last three months. There was progressive anorexia and occasionally dark urine and light stools. Examination revealed a chronically ill-appearing male with evidence of recent weight loss, scleral icterus and an ill defined slightly tender right upper quadrant fullness. The lungs

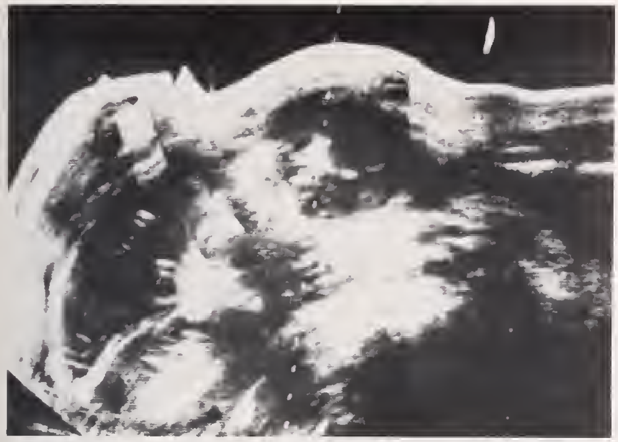

Fig. 1A. Transverse B-mode ultrasonic scan, 9 cm above the umbilicus, reveals a sharply demarcated 3 × 5 cm mass immediately under the liver edge, containing numerous irregular echoes. There is no evidence of gall stones or dilatation of the intrahepatic bile ducts.

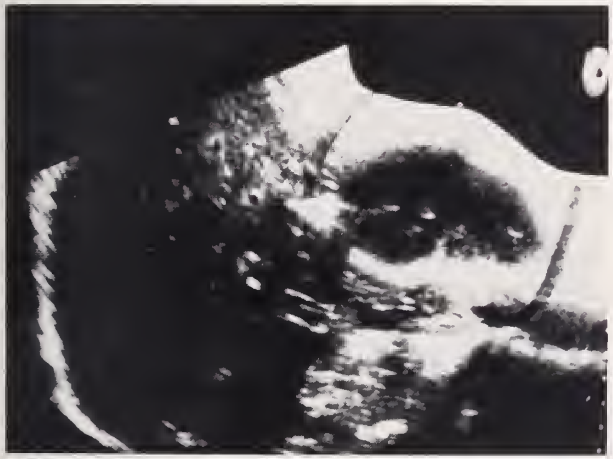

Fig. 1B. In the longitudinal axis, 3 cm to the right of the midline, a similar appearance is noted.

were clear, and there was no adenopathy, splenomegaly or ascites. Because of these findings, sonography of the abdomen was performed, which revealed a well defined 3 × 5 centimeter solid mass just under the hepatic edge (Figs. 1A, 1B). The liver echo pattern was normal and no further sonographic abnormalities were found. The findings were believed to represent a solid mass in the region of the gall bladder. Gastrointestinal series was then performed and revealed a large mass invading the lesser curvature of the stomach and causing an ulceration near its center (Figs. 2A, 2B). Barium enema showed the mass to extend to the proximal portion of the transverse colon, whose anterior wall was invaded and ulcerated by the tumor (Fig. 3). At laparotomy, an inoperable tumor of the gall bladder, invading all the adjacent organs and mesentery was discovered. Histologic diagnosis was gall bladder myosarcoma.

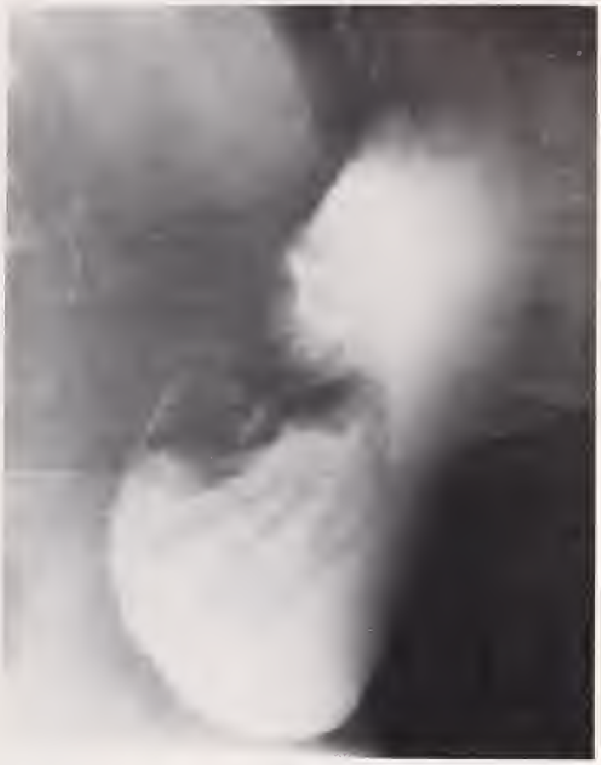

Fig. 2A. Right anterior oblique view of the stomach during the course of a gastrointestinal series, shows that there is a mass invading the lesser curvature of the stomach which presents itself in this partially filled film of the stomach as a combination contour and filling defect. There is a shallow ulceration near the center of the mass.

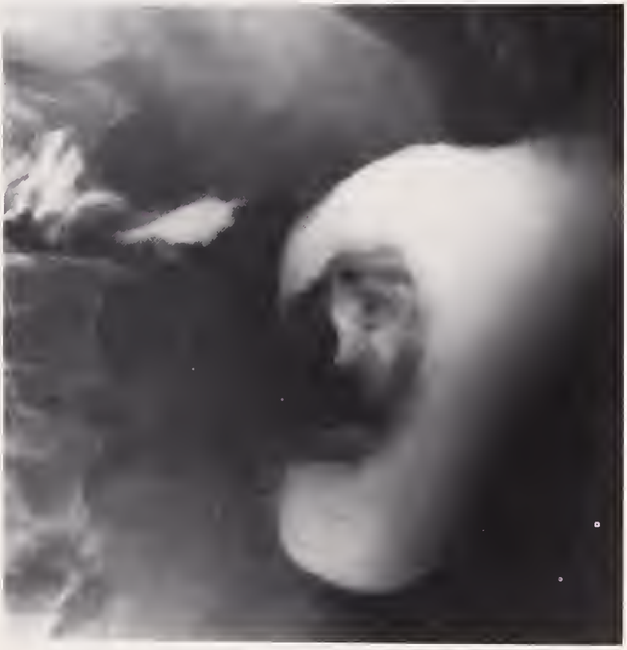

Fig. 2B. A lateral view of the stomach confirms these findings.

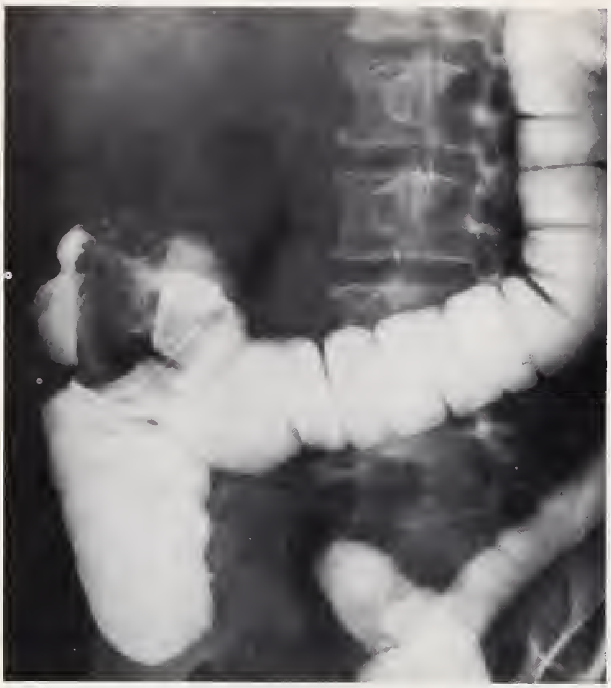

FIG. 3. Left anterior oblique view of the filled colon demonstrates a mass invading the proximal portion of the anterior wall of the transverse colon. There is a shallow ulceration within this mass.

Discussion

Myosarcoma of the gall bladder is an extremely rare disease. The cell of origin is in the muscularis and is similar histologically to those arising elsewhere in the gastrointestinal tract. The microscopic differentiation of sarcomas from anaplastic spindle cell carcinoma may be very difficult. The high frequency of gall stones in the group of sarcoma patients, as well as the same sex and age incidences as in gall bladder carcinoma patients, favors the concept that most of the spindle cell tumors of the gall bladder are in reality carcinomas (1).

Gall bladder malignancies constitute the fifth most frequent cancers of the gastrointestinal tract. A review of 80 series involving 3,930 cases shows the following frequency of the various types of gall bladder cancers: adenocarcinomas 84%, anaplastic 4.6%, squamous cell 4.4%, adenoacanthomas 1.6% and others 5.4% (2). In this latter category are such rare entities as myosarcoma, chondrosarcoma, carcinosarcoma, carcinoid and melanosarcoma (3).

Case Report: Myosarcoma of the gall bladder

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Case No. 403

An asymptomatic 45-year-old white female was referred for computerized tomography (CT) examination of an 8 mm nodule in the right upper lobe (Fig. 1). Eight years previously, a tuberculous infection in the same location was successfully treated medically (Fig. 2). Interval examinations revealed no new significant shadows although a suggestion of a poorly defined nodule partially obscured by a rib could be seen in a retrospective review of a previous film.

Linear tomography in the frontal plane revealed an 8 mm round nodule that was not exquisitely sharp. Some streaky markings in the nearby tissues were consistent with scarring. Calcium was not demonstrated in the lesion (Fig. 3). No other nodules or masses were identified.

CT examination of the upper thorax was performed. Intravenous contrast agent was not employed. The area was first surveyed with a sequence of contiguous 8 mm wide slices. After the lesion was identified, a carefully centered sequence of overlapping 5 mm slices was performed, one of which was directly through the lesion (Fig. 4A). Computerized magnification display of the appropriate area of this slice permitted accurate measurement of the attenuation coefficient of the central area of the lesion (Fig. 4B). The average attenuation coefficient of the central four pixels measured 249 CT units, a high value which indicated the presence of calcium in the lesion. Line printer read-out of the numerical values of individual pixels was also produced which confirmed the high values. The diagnosis of benign granuloma was therefore suggested.

Discussion

See Discussion after Case No. 404

Case Report: Pulmonary granuloma with high CT attenuation coefficient

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(Courtesy of Ramapo Imaging Associates, Good Samaritan Hospital, Suffern, N.Y. 10901).

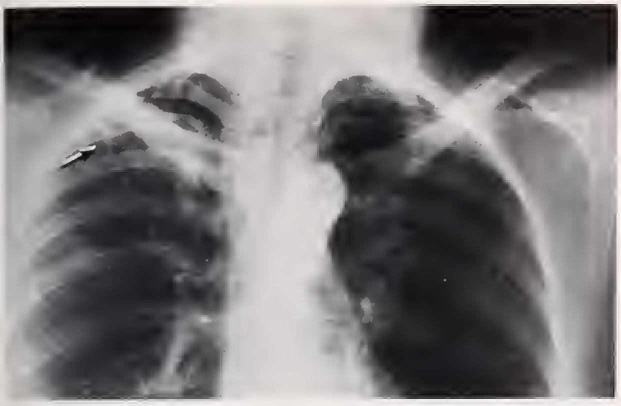

FIG. 1. Posteroanterior radiograph of the chest reveals an 8 mm nodule in the right upper lobe at the junction of the fourth posterior and second anterior ribs (arrow). There is minimal scarring in the nearby lung tissue.

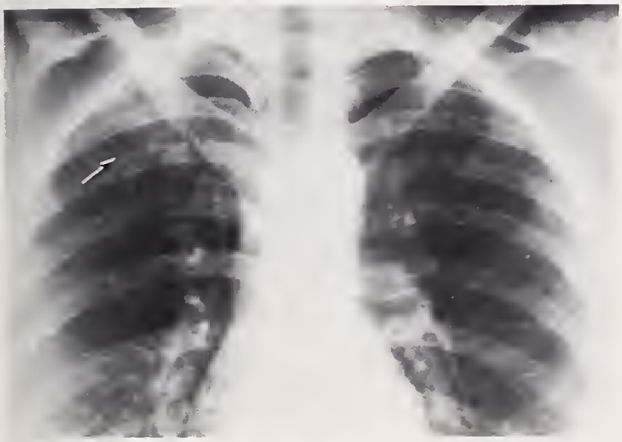

FIG. 2. Posteroanterior radiograph of the chest made 8 years previously reveals an infiltrate in the right upper lobe which represents a tuberculous infection (arrow).

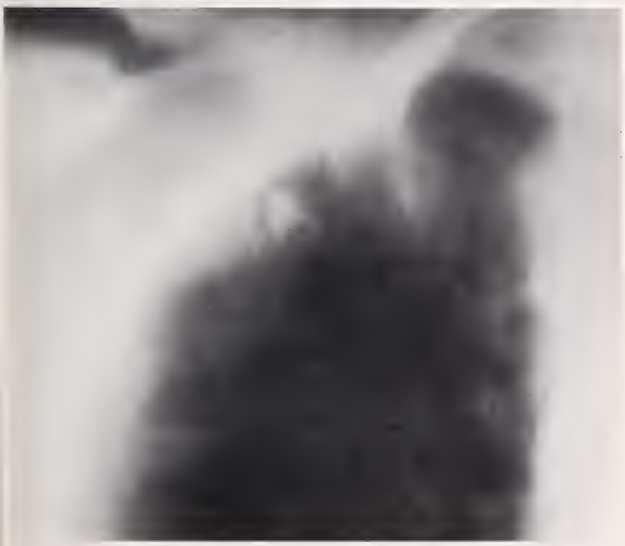

FIG. 3. Linear tomogram (30 degree arc) in the frontal plane through the lesion reveals it to be generally rounded but not exquisitely sharp. Flecks of calcium are not demonstrated.

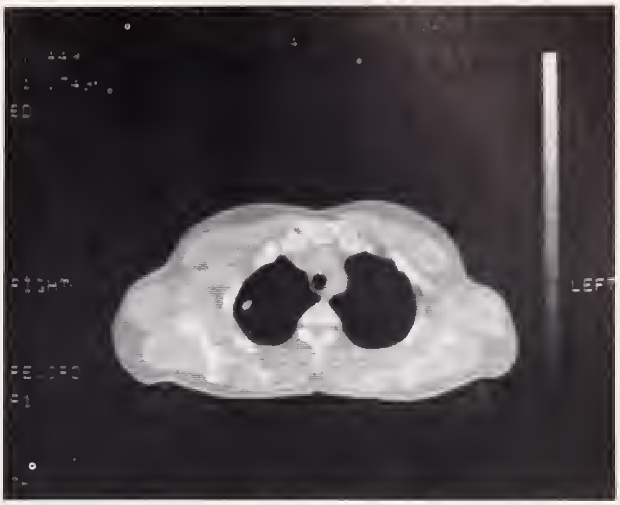

FIG. 4A. Computerized axial tomogram from a sequence of overlapping 5 mm. wide slices is directly through the lesion.

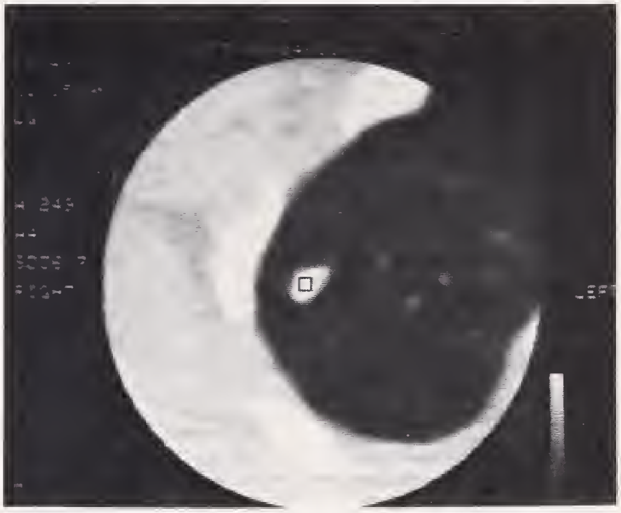

FIG. 4B. Computerized magnification display permits accurate measurement of the attenuation coefficient of the central area of the lesion. The average attenuation coefficient of the central four pixels (black box) measures 249 CT units (standard deviation 36.3). This is a high value which indicates the presence of calcium in the lesion.

Case No. 404

Presented by Robert Lautin, M.D. and Bilha Fish, M.D.

A 60-year-old white female was admitted to the hospital for cosmetic surgery. Preoperative chest films demonstrated a 3cm irregular nodule in the anteromedial basal segment of the left lower lobe abutting the major fissure. (Fig. 1A, 1B). On plain films and linear tomography (Fig. 2) there was no suggestion of calcification. The size, slightly irregular contours, and a peripheral Fleischner line were judged suggestive of primary pulmonary malignancy.

From the Department of Radiology, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, N.Y. 10003.

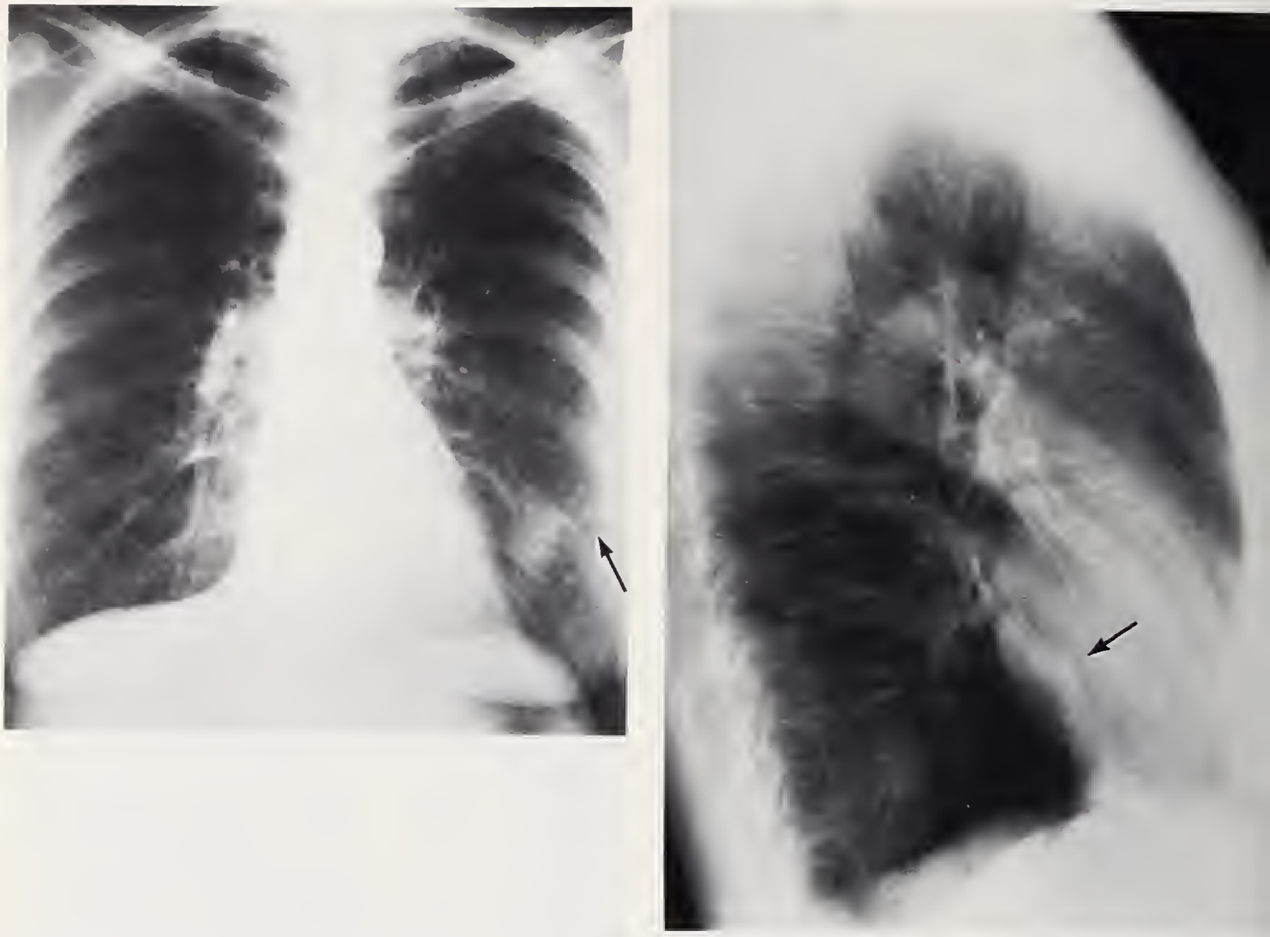

FIG. 1A, B. Posteroanterior and left lateral radiographs of the chest reveal a 3 cm poorly marginated lesion in the anteromedia basal segment of the left lower lobe. A linear density extends laterally from the lesion (arrow), interpreted as a Fleischner line The lesion abuts and bulges the long fissure (arrow).

A CT chest scan was performed. Slices of 1.5mm thickness were obtained through the center of the lesion (Fig. 3) and two separate foci of calcification were demonstrated. CT readings as high as 134 units (on a scale of −500 to +500) were recorded in the foci of highest density (Fig. 4). There was no evidence of hilar or mediastinal adenopathy. Fiberoptic bronchoscopy was normal as were multiple cytologic specimens. Metastatic work-up, including gallium scanning of the chest, was negative.

At surgery a moderately well differentiated peripheral adenocarcinoma was found with the overlying pleura puckered. Left lower lobectomy was performed. Histologic examination with routine H and E staining revealed calcification within cartilage of the terminal bronchi enveloped by tumor. Additional staining specifically for calcium was not performed.

Case Report: Primary malignant lung nodule with calcified foci demonstrated on CT

Discussion of Cases 403, 404

In the evaluation of a solitary pulmonary nodule, the two most reliable criteria for benignancy are lack of interval growth and presence of calcification. The threshhold of perception of calcification has been markedly lowered with the recent application of CT technology to the problem. The utilization of this new modality in evaluating pulmonary nodules has been recently popularized by Siegelman (1). The purpose of this case report is to emphasize that the presence of calcification in a solitary pulmonary nodule detected either by plain film and conventional tomography or solely by CT does not rule out malignancy.

If CT is to be applied to the evaluation of the solitary pulmonary nodule, criteria must first be defined to determine the presence of calcium and, secondly, the significance of calcium when found must be ascertained. Addressing the first problem, Siegelman has postulated, based on his series of 88 cases, that nodules with an attenuation coefficient of greater than 164 Hounsfield

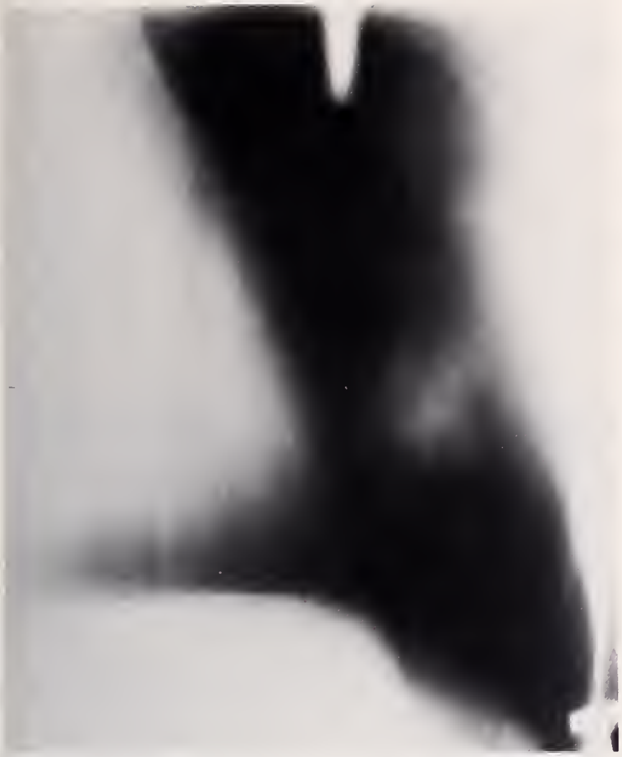

Fig. 2. Frontal plane thin section linear tomography (45 degree arc) through the center of the lesion fails to show calcification.

units are benign and that their higher values are related to the presence of calcium. With our CT instrumentation, the scale of numbers is half that of Hounsfield; therefore, the value of 134 units obtained in the case presented is equivalent to 268 Hounsfield units, well within Siegelman's benign calcified range.

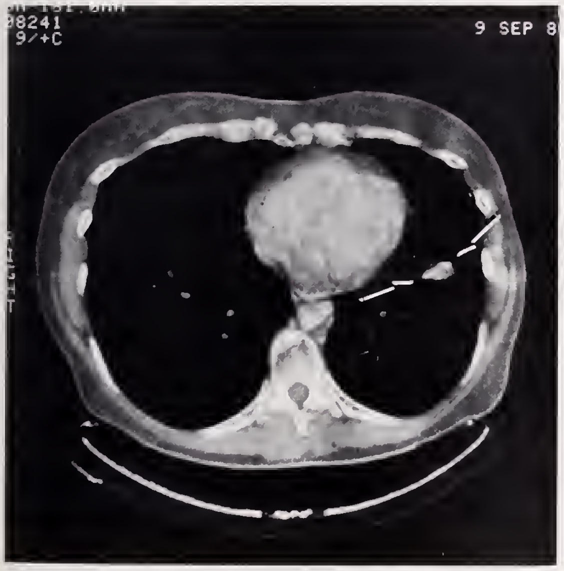

Fig. 3. Computerized axial tomography directly through the lesion (1.5 mm slice thickness) shows two high density foci in the range of calcium (arrows).

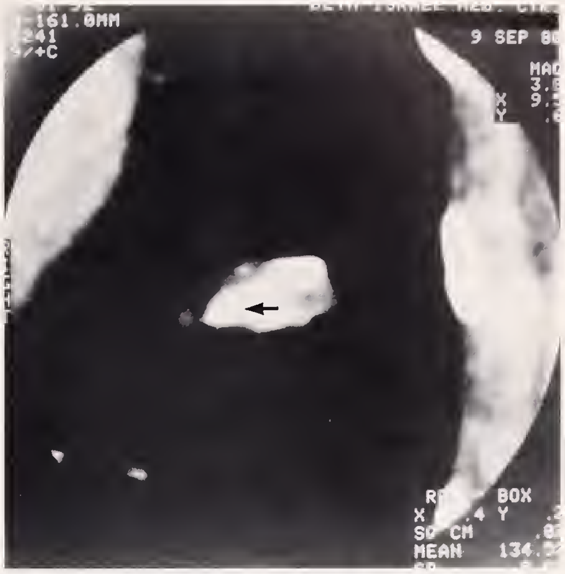

Fig. 4. Magnified display with cursar measurement (arrow points to area of cursar location lost in radiographic reproduction), reveals a CT number of 134.5. This corresponds to 269 Hounsfield units and indicates the presence of calcium.

The presence of calcium in primary malignant lung nodules has been well documented by plain film and linear tomography prior to the advent of CT. Theros (2), in reviewing his material from AFIP, records an occurrence of seven in 1,267 cases. In his series, the etiology in four of the cases was considered to be caused by preexisting postinflammatory calcification engulfed by tumor, and two were considered to be associated with the tumor itself. Theros further states: "The total number that showed calcification would have been considerably higher if an extensive histologic review of all cases had been undertaken." With the current state of the art, CT fits somewhere between conventional radiographic techniques and histologic sectioning in its ability to discern calcification. Using CT, the preoperative percentage of nodules known to be calcified will increase and this increase will include malignant as well as benign lesions. That the degree of increase in the malignant category may be significant is suggested by the case presented.

Prior to CT, calcification on plain films and tomograms suggested benignancy, but the pattern of calcification was of great importance. Central and homogenous diffuse calcification were the two most reassuring patterns in diagnosing granuloma. Siegelman mentions distribution of density as a criterion for judging a lesion and notes that lesions with edges that are dense in relation to the center are suspicious for malignancy. He has not seen this pattern in his benign group of lesions above 164 Hounsfield units. We suggest that the pattern of densities is significant no matter how high the readings.

The nodule in Case No. 404 exhibits the features described by Siegelman. However, it seems likely that in many cases, small deposits of calcium, whether in bronchial cartilage or in areas of previous inflammation, may not be depicted on CT due to averaging with adjacent tissue. When engulfed by tumor and averaged, these preexisting calcific foci may raise CT readings into the benign range. The presence of calcification produced by a tumor and recognized as a discrete focus of calcium by CT will likely be a less frequent occurrence.

Summary

Siegelman, while creating enthusiasm for CT in his article, also clearly expressed many unanswered questions and reservations. In his reported benign group with high CT numbers, he still recommends follow-up films at six-month intervals. We would further suggest that the distribution pattern of calcification, even in the benign lesions, be weighed in the evaluation. Also, other parameters such as size of lesion and characteristics of shape and margins, better delineated by conventional filming and tomography, weigh heavily in determining how aggressively the patient should be managed. One should be especially wary when a nodule is in an area of definite previous inflammation, in which the incidence of benign calcification within a carcinoma might be greater.

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Case No. 405

A 65-year-old man entered the hospital because of hemoptysis. Radiographic examination of the chest revealed a 7cm ovoid lesion in the left upper lobe (Fig. 1A, 1B). During the course of his evaluation, fiberoptic bronchoscopy and cytology failed to produce a positive histologic diagnosis.

Percutaneous transthoracic biopsy of the lesion under CT control was attempted. With the patient prone and with the phase of respiration constant for all slices, the lesion was localized with a plastic grid on the skin and a computer measurement of the distance from skin to lesion center (Fig. 2A). The slice location was marked on the skin using the CT machine's laser localization light and the proposed point of entry chosen with respect to the appropriate grid lines. With respiration momentarily suspended in the predetermined phase, a 22 gauge Chiba needle was introduced to a premeasured depth and a check slice was then obtained to prove that the tip of the

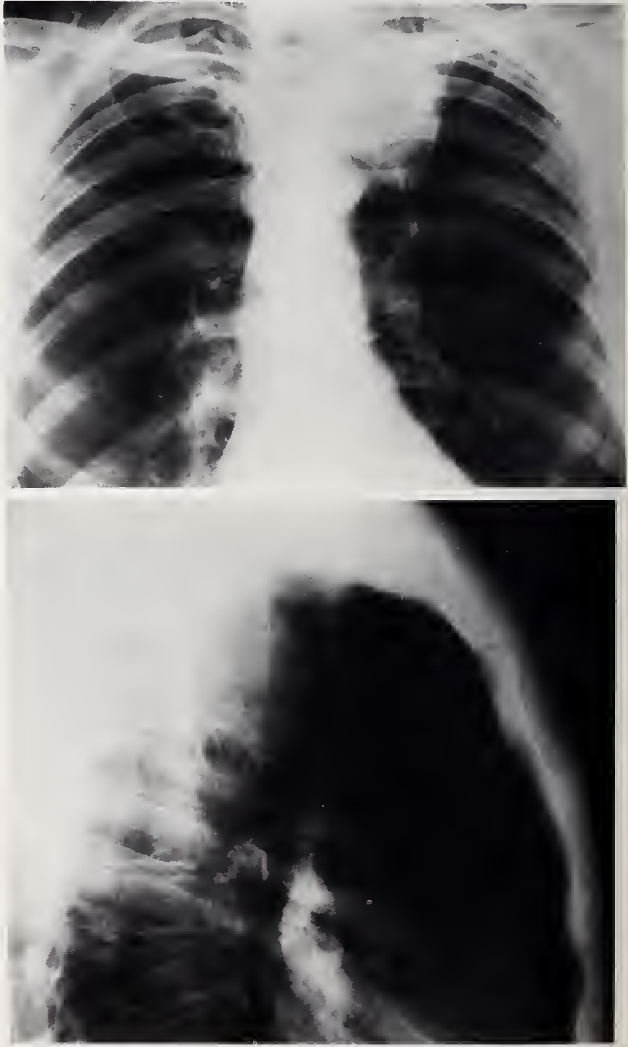

FIG. 1A, B. Posteroanterior and left lateral radiographs of the chest reveal a 7cm ovoid well defined mass in the apical posterior segment of the left upper lobe. The lesion abuts the mediastinum. No other abnormalities are observed. The diagnosis of primary malignant neoplasm is highly likely.

(Presented courtesy of Ramapo Imaging Associates at Good Samaritan Hospital, Suffern, N.Y. 10901.)

needle was located in the lesion (Fig. 2B). Aspiration biopsy was then performed in the usual manner. Histologic examination revealed squamous cell carcinoma.

Discussion

by Melvin R. Shevach, M.D.

In this era of interventional radiology, it is exciting to realize that one can localize and biopsy percutaneously lesions as small as 2cm with rapidity, ease, and a minimum of discomfort to the patient. Significant complications are rare when compared to the morbidity of open surgical biopsy.

Percutaneous biopsy of lung lesions under fluoroscopic control has become popularized since the advent of the 22 gauge Chiba needle. This thin needle technic permits the operator to traverse lung, bowel loops, and blood vessels with relative impunity. CT localization, however, by its exquisite delineation of anatomic detail, is a refinement that enables biopsy of very small lesions and, indeed, even of the active margins of centrally necrotic or cystic lesions (Fig. 3A, 3B).

The procedure consists of placing a plastic lo-

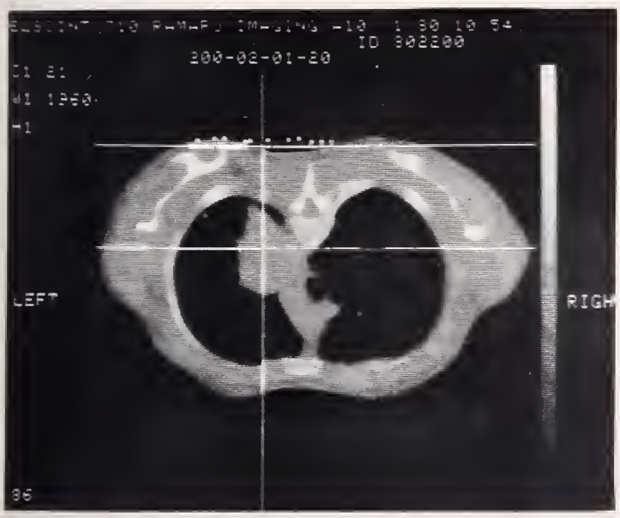

FIG. 2A. Initial CT localization slice through the lesion with the patient prone shows a cross-section of a (homemade) plastic grid on the patient's skin. The depth from skin to lesion center is displayed and measured by computer software. (Note 86 mm recorded in lower left corner of image.)

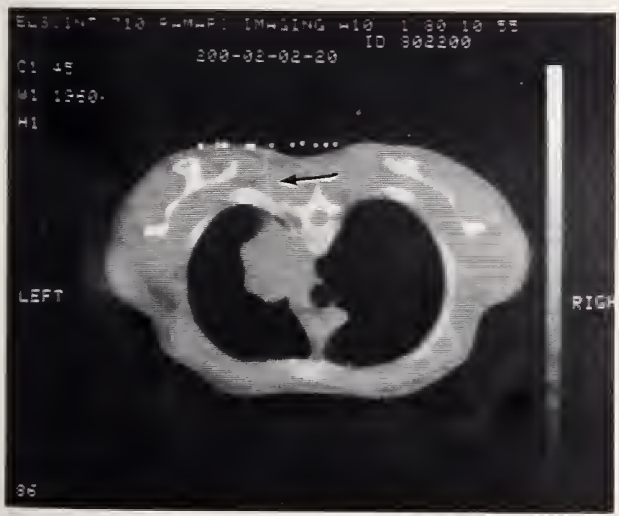

FIG. 2B. After introduction of the needle, a check film is produced to prove that the tip of the needle is in the lesion (arrow).

Care must be taken to avoid a direct hit on the hub of the needle since a large artifact will be generated. There is almost always a slight craniocaudal tilt to the needle and the check slice may be centered just off the needle hub towards the side of the direction of tilt.

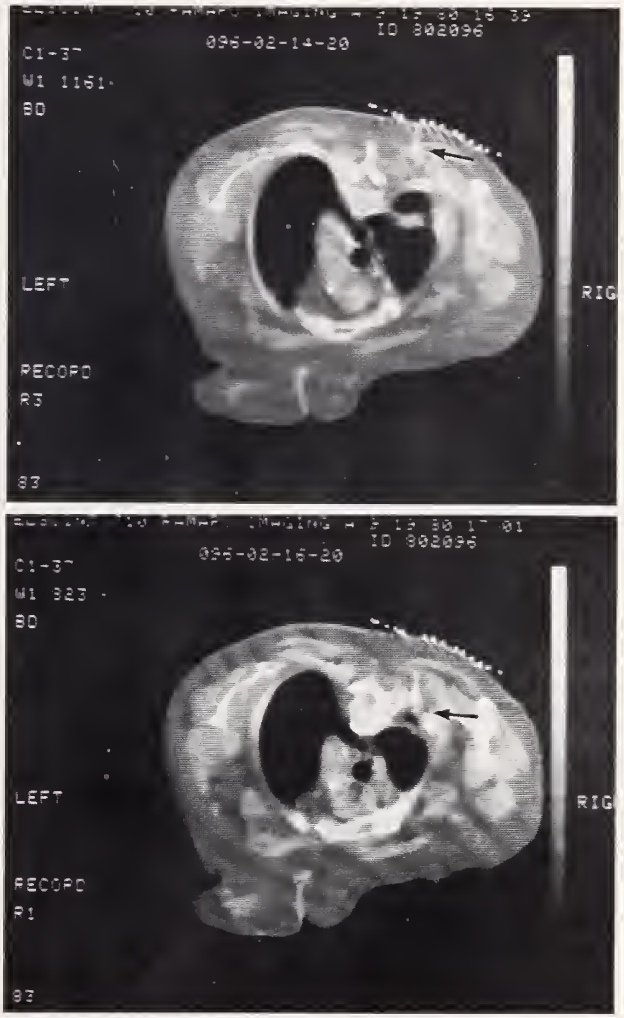

FIG. 3A, B. In another case of a cavitating right apical carcinoma, the first check slice A) imaged only the mid-shaft of the needle due to a significantly angled course in the craniocaudal direction (arrow). A second check slice immediately adjacent B) now reveals the needle tip. Note also the tip of the needle placed in the wall, not center, of the necrotic tumor (arrow).

calization grid over the general area of the chest containing the lesion. The best CT section through the lesion is chosen and the skin overlying the lesion is marked using the laser localization light. It is necessary to consistently reduplicate the phase of respiration during the procedure so as to reproduce the same anatomical section through the patient for the biopsy. In the approach to the lesion, the shortest distance of traverse is usually utilized, but a perpendicular approach is chosen whenever feasible to obviate the need for calculating an incident angle. Bone, of course, must be avoided.

After insertion of the needle, a repeat CT slice is obtained to document the location of the needle tip within the lesion. The stylet is then removed and a syringe attached. During continuous suction, the needle is moved up and down two or three times within the lesion. Suction is then suspended and the needle and syringe are withdrawn. The cytology technician then promptly places the aspirated material on slides and fixes them for interpretation by the cytologist. Accurate cytologic evaluation is critical since the biopsy specimen may contain very few characteristic cells, completely unlike the core of tissue usually obtained for histologic examination when utilizing large bore cutting needles. This difficulty may be somewhat alleviated by the use of a larger 20 gauge needle with a cutting slot, but this carries with it a higher incidence of pneumothorax and presumably of other complications as well.

In our series using the Chiba needle, significant pneumothorax requiring tube aspiration has occasionally occurred but there have been no instances of significant bleeding, secondary infection, or appreciable patient discomfort. Indeed, the ability to biopsy intrathoracic lesions without anesthesia, without significant morbidity, and without the necessity for significant hospitalization, is an exciting accomplishment.

Case Report: Percutaneous biopsy of carcinoma of the lung under CT control

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Miniaturized Afterloading for Brachytherapy of Cancer

(Treatment of Uterine, Breast, and Other Accessible Tumors)

Norman Simon, M.D. and Sidney M. Silverstone, M.D.

It is fitting to commemorate the work of the late Dr. Bernard Wolf with an article on radionuclides. Dr. Wolf's interest in radionuclides started in his early undergraduate studies of physics and his subsequent war-time assignment at Oak Ridge in the days of the development of the atomic bomb. Following his military service, he became Director of the Health and Safety Laboratory of the United States Atomic Energy Commission in New York. From this position, he was invited to return to The Mount Sinai Hospital as Director of the Department of Diagnostic Radiology. During the course of his leadership in diagnostic radiology, he continued his interest in physics and radionuclides. An early paper by Dr. Wolf and one of us (SMS) concerned a study of the focal spot and collimators of x-ray tubes used for radiotherapy. We often discussed radiation problems with Dr. Wolf as we developed the afterloading miniaturized system at The Mount Sinai Hospital during the past 20 years.

Approximately 15 years ago, the miniaturized system of afterloading which we developed in this hospital was first applied to the intracavitary treatment of carcinoma of the endometrium. Cancer of the endometrium had been treated with radium for scores of years by the packing method of Heyman. Professor James T. Heyman was a "machatonim" of Dr. Adolf Lewisohn who was chief of Surgery at The Mount Sinai Hospital 40 years ago. This family relationship provided an opportunity for one of us (NS) to learn the endometrial packing technique with radium under the direct guidance of Professor Heyman himself at the Radiumhemmet in Stockholm in 1949.

The experience of packing the uterine cavity with "hot" radium implanted the nidus of concern in our minds regarding the high radiation dose received by hospital personnel from that technique. Our own adaptation of the Heyman packing method to afterloading continued the efficacy of intracavitary radiation of the endometrium but made the procedure much safer for the personnel treating the patient and for other personnel in the hospital. Our afterloading methods were received with particular comfort by nurses and aides in the OR and recovery room, assisting surgeons and radiotherapists, anesthesiologists, and nurses and aides on the patient floors. The system satisfied the modern prudent attitude toward radiation exposure, that is, ALARA (as low as reasonably achievable).

Afterloading

Afterloading is the placement of hollow tubes into tumors and cavities with subsequent insertion of the radioactive element. The placement of hollow tubes is done unhurriedly in the operating room with roentgenographic check for accuracy. All this is done without any radioactive sources. The radiation hazard for operating room personnel is completely eliminated. The loading of the hollow tubes with the radioactive sources is done in the patient's own room after return from the OR or recovery room.

Radium Substitutes

Radium was the standard radioactive material for the endocurietherapy of accessible cancer from 1900 to 1950. During the past 30 years, many artificial radionuclides have been introduced as substitutes for radium. The search for substitutes was stimulated by the hazards of radium and its decay products. Since the advent of man-made radioactivity, newer radionuclides can be substituted for radium, thereby avoiding the hazards and the difficulties of afterloading radium. We have concentrated on the development of miniaturized sources of cesium 137 as a substitute for radium.

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Miniaturization of Cesium Sources

In 1965, a physicist for a nuclear industrial company developed a method of making sources of ^{137}Cs sufficiently intense to replace radium. These sources were made by repeatedly dipping cylindrical filaments of sponge-like glass (Vycor) into a solution of ^{137}Cs chloride and drying the glass by evaporation so that the precipitated ^{137}Cs is absorbed in the holes of the glass. When this serial dipping and drying resulted in enough radioactivity in the glass source, the glass cylinder was heated to anneal the glass and thereby encapsulate the radioactive material safely and unleachably.

These sources measure less than 1 mm in diameter and we have found them to be free of radioactive contamination during their clinical use for the past 15 years. The process described for concentrating and encapsulating radioactive material in glass is now one of the practical proposals for the commercial safe disposal of radioactive waste from nuclear industry. Our own adaptation of the ^{137}Cs sources allowed us to patent the afterloading Heyman capsules for packing the endometrium. It also led to our miniaturized cervix system which can safely be inserted without anesthesia in the treatment of cancer of the cervix.

Treatment Methods

The techniques of brachytherapy or curietherapy are most applicable in cancer of the uterus, breast, prostate, and in all tumors that are accessible for implantation.

In appropriate stages, cancer of the uterus, both cervix and endometrium, are curable by radium or its substitutes. Development of miniaturized ^{137}Cs afterloading devices at The Mount Sinai Hospital during the past 15 years has resulted in a system which permits simple insertion, safety for personnel and patient, and therapeutic efficacy. The absence of exposure to radiation in this afterloading system makes it more effective for training residents. More than 200 institutions now use this system.

Case Reports

Case I: A 37-year-old mother of six children had a biopsy of a 1.5 cm ulcer at the cervical os, a squamous cell carcinoma. The biopsy was made in the outpatient department (OPD) of The Mount Sinai Hospital (MSH) after a Class IV Pap smear was obtained in a Medicaid clinic in Harlem. The patient was admitted to MSH where her uterus was sounded at 6 cm, and a metallic tandem 4 mm in diameter and 30 cm long was inserted into the uterus after a 16F Foley catheter with a 5 ml bag had been inserted in the bladder. Then a doughnut-shaped plastic inflatable colpostat was placed against the cervix, the tandem being in the hole in the doughnut. Attached to the doughnut were two plastic ovoids, one for each lateral fornix. The ovoids measured 2 cm in diameter each containing three afterloading tubes. The doughnut was inflated with 20 ml of the same radiopaque (KI) and colored (methylene blue) solution which had been used in the 5 ml bag of the Foley catheter. Orthogonal x-ray films of the pelvis assured satisfactory position. The patient was returned to her room where the "dummies" in the afterloading tubes were removed and replaced by radioactive sources, 60 mgm of Ra equiv in ^{137}Cs with an active length of 6 cm in the intrauterine tandem, and 10 mgm Ra equiv in ^{137}Cs in each of the six tubes in the vaginal ovoids. After 50 hours, the system was removed. The exposure dose was 6000 mgm hrs of Ra equiv in ^{137}Cs. The estimated dose at point A was 6000 rads. After a hospital stay of only two days—and no anesthesia—the patient returned to her home to be followed. Five years later, this woman was NED. There was a mild fibrosis and telangiectasis of the vault of the vagina.

Case II: An obese 70-year-old woman with hypertension and diabetes was admitted to MSH for vaginal bleeding. A Pap smear was "negative" in her doctor's office. Despite her fragile condition, a fractional D&C was done under general anesthesia. The cervical canal was free of tumor, but dilatation of the cervix resulted in an outpouring of fragments of tumor which were reported as adenocarcinoma by frozen section. Eleven afterloading Heyman capsules were packed into the endometrial cavity. An inflatable plastic colpostat was placed in the vaginal vault with the hollow tubes from the Heyman capsules lying in the hole in the doughnut of the inflatable plastic colpostat. The ends of these afterloading tubes and the tubes in the ovoids (see Case I) extended through the introitus to lie along the inner aspect of the thigh. On completion of the operation and before ^{137}Cs was loaded into the capsules and tubes, the patient was sent to the recovery room. There her blood pressure rose, and her airway became obstructed. She required considerable medical attention. She finally recovered sufficiently to be returned to her room after the ministrations of at least 12 physicians, nurses and technicians. None of these attendants received radiation exposure. In her room the radiotherapist inserted 11 sources of ^{137}Cs into the uterine capsules, ten measuring 1 cm in active length, each with 10 mgm Ra equiv in ^{137}Cs. A 6 cm source containing 60 mgm Ra equiv was inserted into the remaining capsule and tube. Two 10 mgm sources were loaded into the ovoids, in the vault of the vagina, one on each side of the cervix. The dose administered corresponded to three times the single Heyman dose (30), and the system was removed in less than 48 hours. The procedure was tolerated without incident except for the problem in the recovery room. On follow-up examination, no vaginal bleeding occurred. The patient died from cardiac disease three years after radiation. Had she been a better risk, hysterectomy would have been done following the intracavitary radiation, three years prior to her demise.

Cancer of the breast can be treated by external radiotherapy with a booster dose by implant of radioactive material. Iridium-192 is the radionuclide most popularly used for these implants, but disposal of ^{192}Ir after use is becoming an increasingly difficult problem. Cesium-137 can replace ^{192}Ir now that sources of ^{137}Cs can be safely encapsulated and miniaturized for afterloading in the form of hypodermic tubing of specific length. Early diagnosis and slow growth rate make breast cancer treatment by lumpectomy and radiation a feasible method of control of this tumor.

Case III: A 42-year-old wife of a breast surgeon felt a mass in her right breast. She was in a panic because of her family history. Her older sister was currently under chemotherapy for metastatic cancer of the breast. Her elderly mother had had a radical mastectomy followed by radiation 25 years previously. She survived with disabling lymphedema of the arm. A lumpectomy was elected; 3x4x5 cm segment of breast was excised and reported as duct cell carcinoma, estrogen receptors positive. The tumor was 1.5 cm in diameter. The axilla was not explored. The patient then elected primary radiotherapy, especially requesting that the treatment be given in such fashion that her anxious sister and mother not know of her disease. In four weeks, the breast (mid plane) received a dose of 4000 rads, tangential, no bolus. And the axilla and supraclavicular regions received the same dose through an anterior direct field, care being taken to avoid overlapping of fields. After the external cobalt teletherapy, the patient was admitted to the hospital for a booster implant, 2000 rads in two days, using Henschke plastic tubing in an array of six parallel lines with 1 cm spacing, ends uncrossed. The implanted area included the bed of the excised tumor and the tubes were parallel to the wound. The plastic tubes were placed by first inserting 17 gauge needles using local anesthesia at the line of insertion and exit sites of the needles. Radioactive material used was ^{137}Cs, slender cesium sources, each 5 cm in active length and 1.0 mm OD. The sources were sheathed in platinum and were part of the permanent stock of radioactive material in our "radium room". There was no need to order special radioactive material for this case. The patient was discharged from the hospital immediately upon removal of the implant. Six months later, the involved breast was slightly smaller than the other, the skin was dry, a thickening under the wound seemed unchanged, and no nodes were palpable in the axilla. The patient was informed that attempt had been made to limit the radiation to a tolerable dose, that close follow-up was mandatory because of an appreciable incidence of persistence or recurrence of tumor after primary radiotherapy and that mammography when indicated adds no significant radiation exposure to the breast.

Cancer of the prostate is treated by numerous approaches, and implantation of radioactive material is under considerable recent clinical testing. One of these approaches consists of insertion of iodine-125 seeds along with dissection of the iliac nodes. Its superiority over other methods is still under appraisal. Another technique still under development by us is the implantation of an array of parallel tubes for afterloading with ^{192}Ir or ^{137}Cs.

Cancer of the tongue has been treated for more than 75 years with Ra needles but now the newer afterloading techniques with ^{192}Ir seeds or ^{137}Cs slender sources are replacing the classical Ra needles in the treatment of this tumor.

Flexible sources of radionuclies are adaptable for insertion in cancers of the anus, vagina, penis, parametrium, skin, and lip. These sources have also been used to irradiate residual tumor after attempt at extirpation.

When Cobalt-60 and other megavoltage external radiation devices came into popular use in 1950's, brachytherapy became somewhat less frequently used. But now implantation of the primary tumor appears to be returning to favor because of the newer radionuclides and afterloading techniques. Significant in this return of brachytherapy is the new enthusiasm for implantation of cancers of the breast and prostate, two of the commonest malignant tumors.

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An Unusual Case of Thyroid Carcinoma Metastasis to the Posterior Fossa

IN SOOK SONG, M.D., KAM F. CHAN, M.D., PETER H. TEY, M.D., AND HO-SOON H. CHOI, M.D.

Abstract

A 23-year-old male is presented with a metastatic lesion to the dura mater of the cerebellopontine angle of the posterior fossa from an occult thyroid carcinoma. The mode of spread and the differential diagnosis of the tumor based on angiographic findings are discussed.

Introduction

Although thyroid carcinoma often presents initially as a metastatic lesion while the primary lesion is still unknown, the sites of metastases are generally the lungs and the bones (ribs, vertebral column, and skull). When the skull is involved, the cranial vault is a common site. Often a pulsating mass may invade the epidural space, but the dura forms a barrier to further intracranial spread (1).

The present report describes a patient in whom the metastatic lesion from a thyroid carcinoma invaded the dura mater presenting an extra-axial mass in the posterior fossa.

Case Report

A 23-year-old black male was transferred from another hospital with a three-month history of persistent headache in the left occipital area and also one episode of loss of consciousness. The past history revealed previous heroin abuse and hepatitis.

Physical examination showed the patient to be in no distress. The neurologic examination was also essentially unremarkable. Skull radiographs and tomograms revealed a lesion eroding the medial and inferior portion of the petrous ridge sparing, however, the internal auditory canal.

CT Scans showed a large, irregular and densely enhancing mass at the left cerebellopontine angle suggesting a meningioma (Fig. 1, A-D).

Cerebral angiography was performed to confirm the diagnosis and to ascertain the nature of the tumor as well as to visualize the feeding vessels (Fig. 2, A-E). The external carotid angiograms revealed numerous feeding vessels from the posterior branches of the middle meningeal artery, branches from the ascending pharyngeal artery, the posterior auricular artery and the superficial occipital artery. There was a persistent and dense homogeneous stain primarily at the superior portion of the tumor (Fig. 2A, 2B).

Posterior fossa angiography with injection of the left vertebral artery showed numerous feeding vessels from the large anterior inferior cerebellar artery, branches of the posterior inferior cerebellar artery and the posterior meningeal artery (Fig. 2C 2D). Again a very dense homogeneous stain persisted throughout the venous phase with large dilated veins at the periphery of the tumor (Fig. 2E). There were early draining veins some showing aneurysmal dilatation indicating arteriovenous shunts. The diagnosis was thought to be a left cerebellopontine angle meningioma.

Preoperatively, the lesion was embolized with gelfoam via the ascending pharyngeal artery; the patient then underwent a left occipital craniotomy. A large lobulated, bluish and vascular

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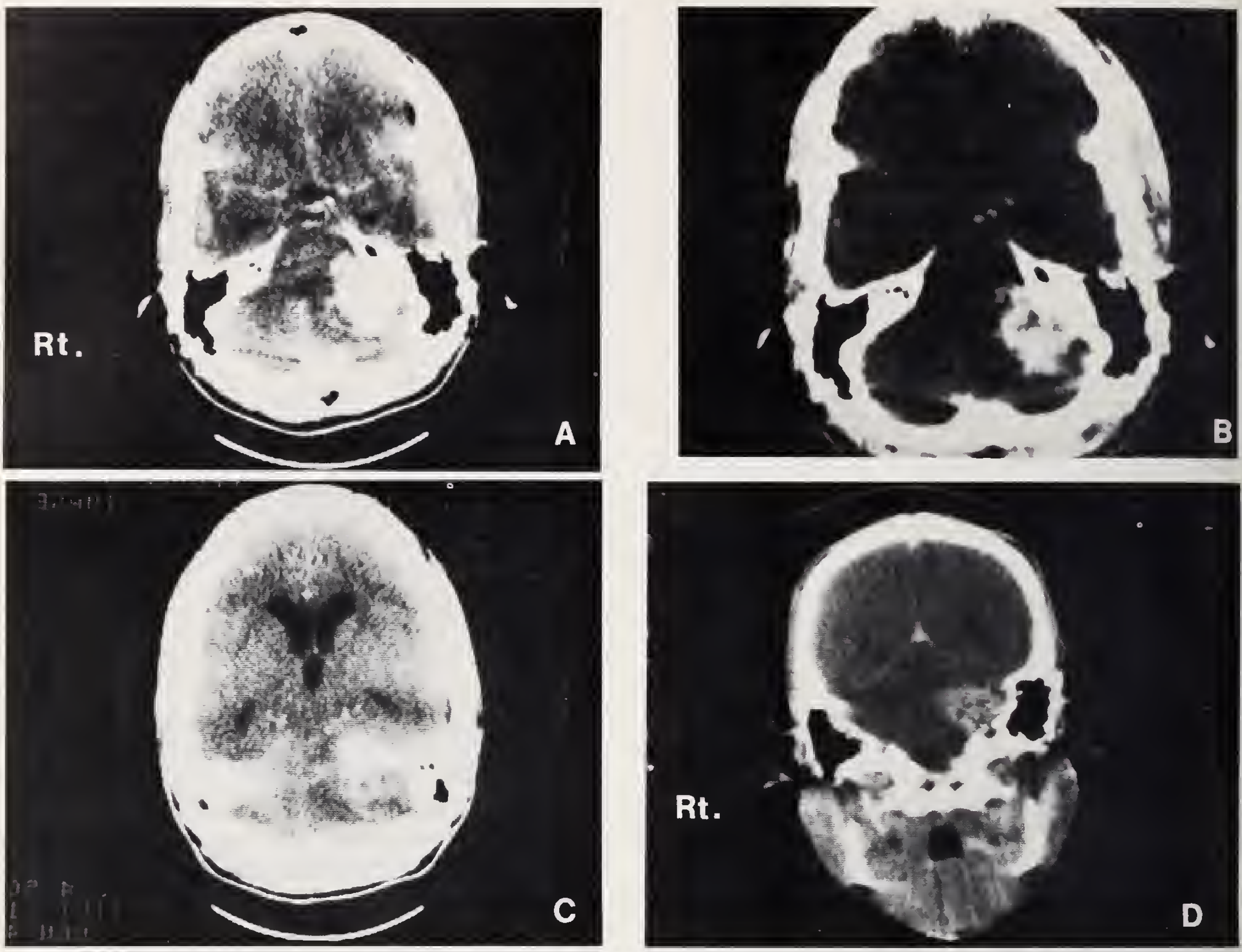

Fig. 1. A large enhancing mass at the left cerebello-pontine angle was noted near the medial edge of the petrous bone in the axial (A, B & C) and coronal Scans (D). There was a small cystic portion at the superior aspect of the tumor (C). The ventricles were slightly dilated due to the posterior fossa mass; the 4th ventricle was shifted to the right (arrow A).

mass was found. The tumor was partially resected, leaving 25% of the bulk near the venous structures. The histologic diagnosis was a metastatic follicular carcinoma of the thyroid (Fig. 3A).

Thyroid scans and bone scans obtained were negative. X-ray studies revealed no additional skeletal lesions. About seven weeks postcraniotomy, a total thyroidectomy was performed. Histologic examination revealed a 3 mm follicular carcinoma with irregular nuclei in many cells (Fig. 3B). The cell type was similar to that obtained from the posterior fossa tumor. Postoperatively, the serum T3 and T4 began to drop, the TSH however rose to 80. Clinically, the patient became myxedematous with weight gain, slowing of speech, slowing of mentation and a rise in serum cholesterol. Several head and neck thyroid scans were again obtained under autogenous TSH stimulation. These showed activity in the right cervical area in which were presumed to be remnants of the thyroid gland; the CP angle tumor however showed no significant uptake.

An ablative dose of 128 mCi of I^{131} was given; 80% of the dose was excreted within 24 hours. The patient was then started on daily Synthroid replacement. At the time of discharge, the patient was euthyroid.

Surgery was again performed six months after the first operation because of failure of treatment caused by the absence of uptake I^{131} at the CP angle.

Discussion

It is well known that thyroid carcinoma often presents as a large metastatic lesion while the primary tumor is still unrecognized (2, 3).

The method of spread of Ca of the thyroid often to distant sites is in all likelihood via the hematogenous route. Batson (4) demonstrated a vertebral venous plexus which consisted of a

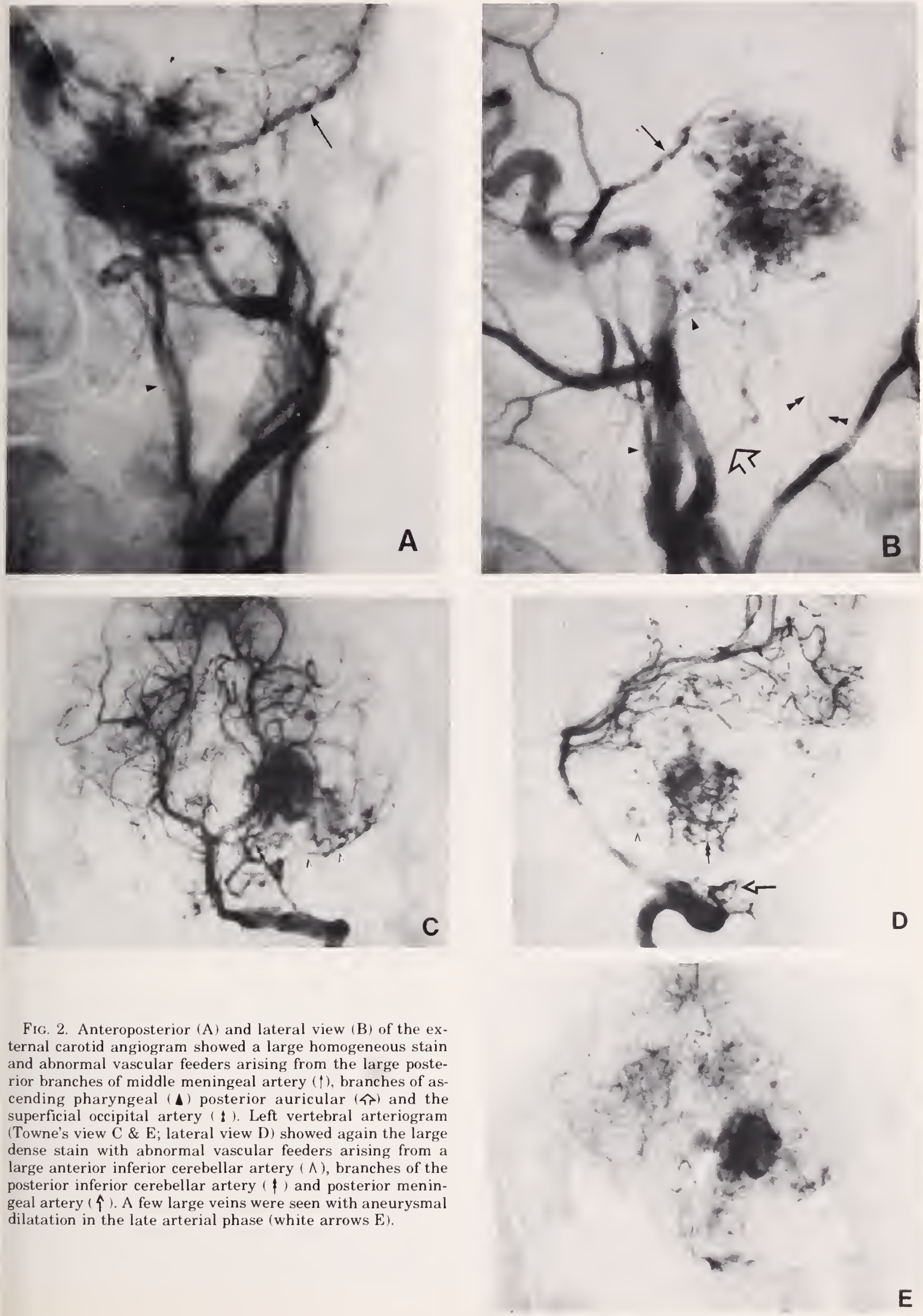

FIG. 2. Anteroposterior (A) and lateral view (B) of the external carotid angiogram showed a large homogeneous stain and abnormal vascular feeders arising from the large posterior branches of middle meningeal artery (↑), branches of ascending pharyngeal (▲) posterior auricular (⇧) and the superficial occipital artery (↟). Left vertebral arteriogram (Towne's view C & E; lateral view D) showed again the large dense stain with abnormal vascular feeders arising from a large anterior inferior cerebellar artery (Λ), branches of the posterior inferior cerebellar artery (↟) and posterior meningeal artery (⇧). A few large veins were seen with aneurysmal dilatation in the late arterial phase (white arrows E).

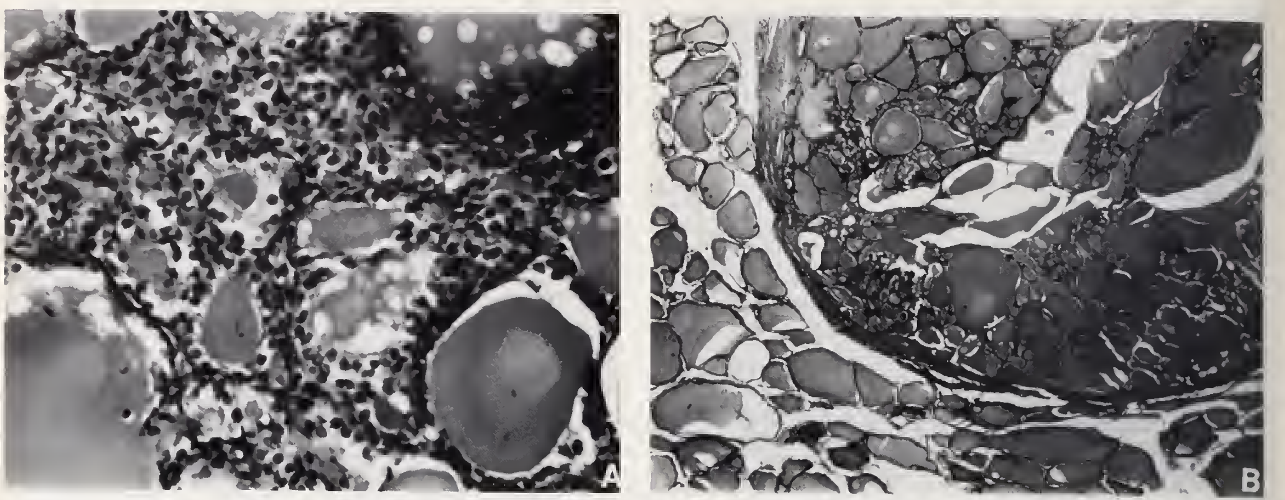

FIG. 3. (A) The metastatic thyroid carcinoma removed from the left cerebellopontine angle showed multiple irregular thyroid follicles containing colloid. The follicles were lined by uniform cuboidal cells having irregular nuclei. (Hematoxylin-eosin stain ×155). (B) The primary carcinoma of the thyroid composed of large follicles lined by cuboidal cells. (Hematoxylin-eosin stain ×40).

valveless vascular bed within the spinal canal and extended from the skull to the pelvis. Both Batson and Eckenhoff (5) showed that there were multiple anastomoses and free connections between this venous plexus and the dural sinuses, the emissary veins of the skull as well as numerous junctions with the cervical plexus. This allowed blood flow to and from the subclavian, the internal and external jugular veins. It is probable that the presence of this venous plexus is responsible for the unusual dural metastasis from the thyroid carcinoma in our patient.

There are few reports describing angiographic findings of metastatic thyroid carcinoma because of the infrequent involvement of the central nervous system. Ito et al (6) reported a case of brain metastasis with angiographic illustrations from a carcinoma of the thyroid. The authors described a highly vascular and densely stained lesion. It was their opinion that the angiographic appearance of the mass would mimick a glioblastoma multiforme if it occurred deep in the brain substance; metastasis to the skull with extradural extension would suggest a meningioma especially if angiography showed a homogeneous stain as described by Taveras and Wood. The same authors also mentioned the occurrence of rapid circulation time in metastatic thyroid carcinomas (7). Passerini et al (1) reported ten cases of metastatic disease from thyroid tumors and "benign metastasizing goitres." They recorded five cases of skull involvement, three cases involving the cranial vault and two cases involving the base of the skull only. Four of the patients were studied angiographically. In each instance, the vascular supply was primarily from the external carotid artery. There were numerous neoplastic vessels and arteriovenous shunts. In one patient, the angiographic appearance was reported to be identical to a sphenoid ridge meningioma. Ripp et al (8) reported a case of metastatic thyroid carcinoma to the mandible which was initially thought to be an arteriovenous malformation.

In our patient, the large highly vascular mass in the cerebellopontine angle received its blood supply primarily from branches of the external carotid and of the vertebral artery. The angiographic findings were very similar to a cerebellopontine angle meningioma except that there were large early draining veins with aneurysmal dilatation representing A-V shunts, which were confirmed at surgery. While a meningioma usually showed a slow circulation time without arteriovenous shunt compared to a metastatic thyroid tumor, A-V shunting would be more pronounced in a glomus tympanicum tumor and in an arteriovenous malformation. An A-V malformation also would not have presented such a large mass effect as in thyroid metastasis.

Posterior fossa angiography then, has maintained its usefulness despite the advent of computerized tomography not only in the determination of the vascular status of a mass but in the actual differential diagnosis of posterior fossa lesions.

Summary

To our knowledge, this 23-year-old male with an occult primary cancer of the thyroid, represents the first report of dural metastasis with CT and angiographic findings. The large extra-axial

metastatic tumor involving several cranial nerves (7th, 8th, 9th, 10th and 11th) while the temporal bone was only minimally destroyed suggested that the prime metastatic site was the dura rather than the osseous structures—a most unusual feature of thyroid metastasis.

Acknowledgments

The authors wish to dedicate this case report to the memory of Professor Bernard Wolf whose many and varied contributions to Radiology have greatly inspired us.

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Breast Imaging: Past, Present and Future

Philip Strax, M.D.

Preface

Dr. Bernard Wolf was involved in the initial studies of mammography in breast cancer. His encouragement was very helpful in promoting the efforts described below. It is most appropriate that this article be offered in tribute to his memory.

This paper is dedicated to Adam, the first man to popularize inspection and palpation of the female breast, the first to evaluate subcutaneous breast structure as we now see it on mammography and ultrasound and the first to appreciate the infrared emanation from the breast which is now embraced in thermography.

Over the years, many investigators, including physicians, have followed Adam's lead in the attempt to discover breast lesions. Many physicians have, of course, developed remarkable proficiency in detecting even small tumors. To this day there are still clinicians who insist that their fingers can tell them the truth about breast lesions. They say, "If I can't feel the cancer, it isn't there."

Since the breast is readily accessible to clinical examination, why do we need breast imaging with different modalities to ferret out pathology? Consider the following:

1. The breast is naturally multinodular and the difficulty of detecting the small nodule of an early cancer midst the many other normal lumps becomes apparent. Mammography has had a long history of being able to make an important contribution to this problem. The mammogram has turned out to be our most useful modality that very often—but not always—gives the physician the additional information he needs to know as to whether the lesion is malignant or benign. It is often the added bit of suspicion that leads to prompt exploration.

2. Even with the presence of a definite lesion on clinical examination for which exploration is contemplated, the mammogram offers additional information on the condition of the surrounding breast tissue or that of the opposite breast. A cancer, which is nonpalpable, may be lurking elsewhere in either breast and that other lesion may be the cancer, not the mass leading to exploration.

3. Perhaps the most cogent reason for mammography in the symptomatic woman who feels a vague mass, localized pain or nipple discharge is the varied expertise of physicians in breast palpation. A mammogram under such conditions may be life-saving in avoiding delay.

4. More importantly, a breast cancer may not be palpable by even the most expert hands and still be in the early stages of a deadly disease. It has been known for many years that the breast may harbor an occult cancer, completely asymptomatic and nonpalpable, detectable only on mammography.

It should be emphasized that because neither palpation nor mammography is 100% accurate, if a cancer is suspected on palpation a negative mammogram should never be allowed to delay exploration of a breast. Similarly, a clinician who is faced with negative clinical findings, but with a positive mammographic report, should seriously consider exploration. The two modalities are truly complementary. They should never be considered competitive.

5. Mammography is an excellent tool that can help in differentiating the benign from the malignant lesion. As such, it can occasionally avoid or delay unnecessary exploration, and it can expedite surgical intervention when needed.

Usually, benign masses are well circumscribed, round or oval, and lobulated. They extend into their milieu, displacing the breast elements but not invading them. These masses are homogeneous in density, occasionally containing large, regular, scattered calcifications, within the mass in fibroadenomas or in the periphery in cysts.

Benign cysts are common, especially in women from 35 years of age up to the time of involution. They often are multiple and bilateral and may

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exhibit thickened walls because of inflammatory change. Many cysts are visible on the films and not palpable, but the opposite also is true.

The primary signs of malignancy are:

1. A more or less infiltrative mass.
2. Sandlike, numerous, grouped microcalcifications.
3. Localized area of trabecular distortion.

The malignant mass usually invades its surroundings with distortion of the structure of the breast and usually is irregular, ragged, and spiculated, with a poorly circumscribed border.

The microcalcifications that appear in a group like grains of sand or salt often are small and uncountable and may be present on the mammogram without evidence of a mass. They represent necrotic, intraductal material and may be present in nonpalpable or preclinical cancer. The importance of such microcalcifications is that they usually are found without axillary node involvement and with a better prognosis.

Mammography has been of particular value in detecting malignancies on the basis of these microcalcifications present in approximately one-third of the cases. It also can detect small infiltrative densities in the large fatty breasts so common in the postmenopausal patient, in whom clinical examination is difficult.

Altered architecture may be the only clue to malignant change. Fine changes of trabecular distortion or localized areas of fibrosis, especially when associated with haziness due to edema, may be the earliest signs of cancer even in the absence of a mass density.

Recent years have seen a dramatic improvement both in the quality of mammography and in the radiation dose used. The most widely used technique, purporting to produce the highest quality, in the 1960's was that of Egan (1), involving a slow industrial Kodak type M film, a tungsten tube, close coning, no compression with low kilovoltage and high milliampere-seconds. This technique produced mammograms with radiation doses ranging from 7−12R to the skin per examination. In the last few years, under the leadership of British radiologists like Price et al (2), and Ostrum et al (3) among others in the United States, the use of faster film-screen combinations in vacuum cassettes has demonstrated a remarkable improvement in contrast and resolution of the mammographic image plus a reduction in radiation levels to .2−.3R to the skin. The latest measurements by Daniel Miller and associates (4) indicate that such skin radiation, with the low kilovoltages used plus the molybdenum-anode tubes and compression techniques, is delivering doses to the mid breast of .02−.03 rads for a right angle pair of films. These techniques are readily available and are being used by an increasing number of radiologists.

Xeromammography as developed by Wolfe (5) and others has also been used effectively in the past 15 years with production of excellent mammograms. Here, too, changes to the negative mode and increased kilovoltage have resulted in reduction of radiation, though not near the low levels attainable by the newer film-screen techniques.

The discussion of benign vs. malignant changes in the breast is appropriate in considering mammography as a differential diagnostic tool. In this context, reference is made primarily to the woman who detects a breast abnormality which propels her to her primary physician. When we consider that such a woman may indeed have a cancer, all manner of examination is appropriate at the time when signs or symptoms are apparent. Mammography, of course, with the best current technique is usually necessary in addition to clinical examination or any other modality available to the physician.

In recent years, there has been increasing awareness that mammography is particularly important in mass screening because of its potential in finding nonpalpable cancer. The mass screening approach for the control of breast cancer is based on the following;

A. Breast cancer is one of the most important medical conditions confronting women and their primary care physicians. This disease has had an increasing incidence in this country accounting for 28% of all cancers in women. It now attacks one women in 11. There has been a stationary death rate from the disease for the past 40 years.

B. The probability of primary prevention of the disease by a vaccine or by environmental control, such as change in nutrition, is poor for the immediate future. The outlook for a magic bullet or other remedy to cure the disease at any stage is not promising. All we have is the knowledge that absence of axillary nodal involvement at time of surgery, an index of localized disease, is followed by a more than 85% five-year survival rate. With nodal involvement the five-year survival rate drops to about 50%. Earlier detection might lead to treatment of more localized disease. Since most cancer today is not localized when first seen by the clinician, a means must be found to have women present themselves for examination with their disease at an earlier stage than is commonly the case. This means, in a practical way, detection of preclinical cancer in apparently well women when the disease is unsuspected by patient or physician—as is the case in mass screening.

C. This concept is supported by the one-third reduction in mortality achieved in the large-scale screening program for breast cancer detection conducted by the Health Insurance Plan of Greater New York (6), under contract with the National Cancer Institute.

In this study, 62,000 women, randomly selected, age 40–64, were chosen as 31,000 pairs, carefully matched, as a control group and as a study group. This study group, two thirds of whom responded, were invited to have the examinations, which were palpation and mammography done independently. Examinations were given initially and in three annual studies. Since that time, data have been collected.

In a nine year follow-up, 128 deaths from breast cancer occurred in the control group compared to 91 in the study group. A 25% reduction in mortality persists after twelve years of follow-up. There is, therefore, a rational basis for expanding the concept of mass screening to detect early breast cancer as a means for saving lives of the afflicted women.

The role of mammography was emphasized in this study in which all those examined received independent mammography as well as clinical examination. Of all the cancers detected through screening in this study, one third were found on mammography alone and were not felt by palpation. However, it should also be emphasized that two-fifths of the cancers were found on clinical examination alone and were not detected on the x-ray. Obviously, both modalities were necessary for proper diagnosis. It is also important to note that the cancers found on one modality alone had a high percentage of no axillary nodal involvement—79% in those cancers found on mammography alone and 75% in those detected by clinical examination alone. It appears that in early breast cancer, only one modality may be positive in a high percentage of cases. Cancers found on both modalities had the same percentage of positive nodes (over 50%) as in the control group.

It was also noted that the entire reduction in mortality was concentrated in women over the age of 50. Those under 50 showed no such improvement.

D. These considerations led to the development in 1968 of the Guttman Breast Diagnostic Institute in New York City with the basic objective of developing a mass screening approach that would be feasible and could reach the general population of women. One of the major problems to be solved was how to develop a practical, economical and efficient method that could produce a satisfactory yield of earlier cancers. Up to 50,000 examinations per year are made in cooperation with the American Cancer Society of New York City women without charge.

E. With the Guttman Institute as a prototype, 28 other screening for breast cancer programs have been funded by the National Cancer Institute and American Cancer Society in the United States, including Hawaii. In all of the centers, substantial numbers of breast cancers have been found, with a high percentage of no axillary nodal involvement, up to 45%. There is justified expectation that breast cancer can be detected in a localized stage in a large percentage of cases under mass screening conditions. This should lead to potentially increased survival and saving of lives.

Because in the HIP study no mortality benefit was noted in women under 50, comparison of results in the BCDDP with those in HIP is particularly interesting, especially in women under 50. The data would suggest that the improved mammographic techniques used in the screening centers resulted in substantial improvement in yield of localized cancers in women under 50 and boded well for mortality reduction in this age group.

Because of concern about x-radiation in relation to the breast and because of the possibility that other modalities might increase the yield of cancers and perhaps reduce the rate of "interval" cancers, there has been increased interest in the use of modalities, like thermography, ultrasound and improved methods of transillumination.

Thermography, as introduced by Lawson (8), is a pictorial representation of the heat that emanates from the breasts. It is a physiologic and not an anatomic determination. This increased heat in one breast compared to the other may be due to a variety of causes, including cancer. Most cancers are associated with increased heat. Thermography is thus really a "red flag" that alerts us to the possibility of a disturbance which may be cancer.

Because increased heat is associated with various breast conditions that are not cancer, approximately 15% to 20% of women have positive thermograms without positive findings on the other modalities. We consider such women as potential problems and reexamine them every six months instead of every year. Thermography may thus be a high risk marker.

Thermography may also have prognostic value in the presence of malignancy. Several workers have found a substantial proportion of proved cancers with preceding "cold" thermograms. It is now becoming apparent to investigators that the "cold" cancer has a better prognosis than the "hot" one. We may be recording the metabolic activity of a carcinoma. The one with the greatest heat as seen on the thermogram may be the more aggressive one.

The drawbacks of thermography are as follows:

1. It does not indicate the location of a cancer, as does palpation or mammography. The heat is transmitted from the cancer by way of blood vessels, and the area of increased heat may be far removed from the cancer. Operation is done only when the location of the cancer is indicated by palpation or mammography.
2. The most important problem with thermography is that it is normal in some 25% of women with proven cancers. Even more, most of the undetected malignancies are in a nonpalpable or minimal stage. Therein lies the real reason why thermography cannot be used as a sole screening modality (9).

In short, the accuracy of thermography should not be compared with that of palpation or mammography. The latter two are anatomic markers, while thermography is a physiologic one. As such, its help is additive and complementary, not competitive.

Improvements in thermography are being directed to the use of cholesterol crystals and to making the modality more objective than it has been to date. A method of graphic stress telethermometry, in which objective multiple point heat measurements are made before and after stress with hands in ice water shows promise, according to early investigators, of making thermography more objective. Further studies, however, are needed to evaluate the procedure with other proven modalities to answer the fundamental objections to thermography.

Ultrasound has been used in breast diagnosis for several years. It has shown a definite potential in differentiating a fluid-containing cyst from a solid tumor. It has been disappointing, however, in detecting lesions under 1cm in diameter. New studies with improved equipment, particularly that of Kossoff (10), as used by Goldberg in Philadelphia, and that of Wagai (11) in Japan, show promise of becoming valuable detectors of small cancers and replacing or supplementing mammography in special instances.

Diaphanography is a new sophisticated method of transillumination using a special light source with infrared film. A high degree of accuracy has been claimed by its Swedish developers. The device is under study in several institutions and may be of value in cancer detection. It is being evaluated by Isard in Philadelphia who feels the device has merit in differential diagnosis but is probably not adequate for mass screening (12).

The Mammoscan is a device invented at the Weizmann Institute in Israel which can electronically detect a mass. This may prove to be useful as a palpation modality. It is in the process of evaluation in Switzerland and possibly at the Guttman Institute.

In recent years, physicians and their patients have been subjected to a barrage of innuendoes and conflicting statements about the use of mammography in detection of breast cancer, based primarily on an appraisal by Bailar (13). Many women—and their physicians—have been led to the conclusion that mammograms, even one mammogram, can start the development of a breast cancer. The average woman exposed to such a concept is then caught in a dilemma: she has been taught that detection of early breast cancer is the best method to reduce the stationary death rate from breast cancer and that mammography plays a most important part in that detection. At the same time, she has developed increasing anxiety that the mammography, even if performed by a recognized radiologist, may in itself give her the disease. It is becoming our responsibility to overcome the hysteria that has been engendered. Instead of iatrogenically producing a breast cancer epidemic by using mammography we may be iatrogenically producing a serious drop in survival statistics by *not* using mammography to detect early disease. The seriousness of the dilemma is that women have equated mammography with breast examination and that many symptomatic women are turning away from their physicians altogether until the disease has become much too obvious.

The only group in which real disagreement on whether mammography is ethically indicated is the one containing women under 50 who are truly asymptomatic. Here, too, there is general agreement that such women, who have the substantial risk factors of previous breast cancer or positive family history in mother or sister, should have a periodic complete examination, including mammography. Of course, since breast cancer is uncommon in women under 35, they should be excluded unless medical suspicion of breast disease warrants mammography.

The problem in the younger asymptomatic women revolves around two facts:

1. The breast is sensitive to x-radiation. Previous studies on women subjected to substantial doses of radiation, such as with the atomic bomb, fluoroscopies in the course of tuberculosis treatment or radiation treatment for breast abscess, have indicated increased incidence of the disease in those exposed. Such breast cancer initiation had a latent period of about ten years and varied in proportion to dose. Although no evidence exists for absence of a threshold dose, it has been considered prudent that such a dose be postulated and that a linear radiation effect be assumed down to the smallest quantity of radiation. A figure of "1 rad to the body of the breast given to a million women would produce six cancers per year for the lifetime of the woman after a latent period of six to ten years" has been offered by Dr. Arthur Upton (14), noted radiobiologist and past director of the National Cancer Institute, as a fair statement of radiation risk from mammography. In addition, he wrote recently: "Since the risk that the average woman will develop breast cancer at some time during her life is roughly seven percent, the incremental risk she would receive from a single mammographic examination performed with the low-dose technique (involving a mean dose to both breasts of less than one rad) would be expected to increase her total risk by much less than 0.07 percent, that is, from a starting level of seven percent to much less than 7.07 percent after the examination. By the same token, the number of such mammographic examinations required to double her risk (to raise it to 14 percent) would be many more than 100. Viewed in this context, the average woman would probably not consider the risks of a single mammogram to outweigh its potential benefits, if she had valid medical or psychological grounds for desiring the diagnostic information it might provide."

2. There has been no evidence to date that the HIP study, using clinical examination and mammography with the techniques considered optimum at the time, has produced any reduction in mortality from breast cancer in women under 50. Whether such a state of affairs would exist in the N.C.I.-A.C.S. screening programs with the improved mammographic techniques being used must be considered pure supposition. Since no control groups are present in these studies, no data on mortality can be expected. This means, in short, that since apparently well women are being subjected to potential radiation hazard in mammography with no potential benefit in mortality reduction from this modality, the hazard presumably exceeds the benefit and should be avoided. That is the nub of the mammography controversy.

In considering the risk vs. benefit in mammography emphasis should be placed on additional factors.

a. In the HIP study, more cancers were found in the study group than in the control group in women under 50, yet the numbers of deaths were the same. Perhaps in women under 50, cancers of the more localized type, found particularly on mammography, might have been detected over the age of 50 if no screening program were available. Perhaps screening women under 50 in that study helped to keep the death rate down in those over 50. This concept is being investigated further. It may elucidate the perplexing question of why mortality benefit was demonstrated only in women over 50 years of age. There is no doubt that a strong hint of benefit has been developed in the BCDDP program that substantial improvement in numbers of cancers found, in small size of these cancers and the increased percentage of negative nodal involvement indicate a potential improvement in the lot of women under 50 with breast cancer. There also have been statisticians, such as Dubin, statistician with New York University Division of Epidemiology and Seidman, head statistician of the American Cancer Society, who have developed mathematical formulae indicating probable mortality benefit in women under 50 in the HIP study. All to no avail. The consensus among epidemiologists is that no mass screening is indicated in asymptomatic women under 50 until a new study directed to this age group is mounted and data collected. Many agree that results will probably point in the right direction, but insist on awaiting results of a new study. One such study is about to be started in Ontario, conducted by Anthony Miller.

Risk is directly proportional to dose. The state of the art in mammography has changed radically in the years since the HIP study. In that study, a dose of 7.7 R to overlapping fields of the skin was given per examination. The film-screen techniques at the Guttman Institute (as measured by the Northeastern Physics Center) deliver a dose of .02 to .03 rads to the mid breast.

National Cancer Institute guidelines formulated in 1977 for use at the screening centers supported by N.C.I. specifically exclude women with *any* symptoms whatsoever. This gray area needs further clarification. When does a lump or a pain or a nipple discharge make a woman symptomatic? Is a single lump a symptom and lumpiness or multiple lumps not? Is a localized persistent pain a symptom and diffuse intermittent pain not? Is a free-flowing dark discharge a symptom and a discharge produced by nipple pressure not? These are important considerations, certainly in the mind of the woman. Minor degrees of symptoms are commonplace. When we consider that most cancers are found under screening auspices, in women under 50 as well as those over 50, with only minimal symptoms or none at all, we can perhaps begin to be more liberal with our interpretation in light of the low dose of radiation to the breast.

The guidelines for the truly asymptomatic woman are as follows:

1. Over 50, mammography should be used as part of the routine medical care of a woman because the potential of saving lives by early detection of a breast cancer far outweighs any possible risk.
2. Between ages 35 and 50, mammography should be used in asymptomatic women only if there is a positive family history or a previous breast cancer.
3. Under age 35, mammography should be used only if there is a previous breast cancer.

The American Cancer Society in its latest recommendations adds that women between 35 and 50 who are asymptomatic should have a base-line mammogram.

Conclusions

There may be reasonable disagreement among the experts on what is a "killing cancer", or what represents a "true" cancer, or how much cancers should be treated, or whether they should be treated at all, or what is the best treatment for an invasive killing cancer of different pathologic types in women of different ages, emotional or psychic backgrounds. But there is general agreement that the earlier a breast cancer is detected and treated, more women will survive the disease and more will be cured. There is also general agreement that early detection involves at least three basic principles:

1. Advancing age is the most important risk factor, since most breast cancer is detectable in women over age 50. There is definite proof in this age group that screening for the disease will lower the death rate by at least 40% and that mammography as well as palpation are necessary for such reduction. It is imperative that screening using both modalities become a routine part of the medical examination of all women over age 50 on an annual basis.

2. Since the symptomatic woman with a dominant mass or a persistent pain or nipple discharge may have these symptoms because of an underlying cancer, all such women should have a complete breast examination to include mammography or any other diagnostic study as often as necessary to make sure cancer is or is not present.

3. Mammographic technique used under all circumstances should be the one producing the greatest detail and resolution, with the lowest amount of radiation needed to produce high quality films. Such techniques should be subject to change as new knowledge and technology provides improvement in these areas. Techniques are readily available and in use that deliver doses down to .02 rad to the mid breast. This low dosage can be considered negligible in comparison with the presumed benefit from mammography.

4. Clinicians should be aware of the limitations of mammography and remember that, after all, the x-ray study of the breast is an ancillary, though most valuable, ally when the clinician is confronted with a patient's breast problem.

5. The greatest value of breast imaging lies in its potential to detect breast cancer in a more curable stage, even before it is palpable. This can be accomplished today by its use in mass screening. Such screening may be difficult but it is our only proven method with potential to reduce the stationary death rate from the disease. Until true primary prevention is developed, it behooves us to continue our efforts to make mass screening ever more efficient, economical and safe.

To sift through many to find the few
Is tiring, costly, hard and slow;
We always seek that something new
To keep the "cost effective" low.

We must detect our breast Ca
With better methods—more and more—
For that's our only hope today
To save more lives than we did before.

To sift through many to find the few
May bore and make one curse his lot,
But 'til we find that something new
Let's do our best with what we've got!

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Problems in Mammography

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Calcifications

The first person to employ radiography to visualize breast tissue was the Berlin surgeon Salomon in 1913. His work was on excised specimens and he was chiefly interested in improving his biopsy techniques. He tried to demonstrate the ramification of breast cancer within the breast, showing how the tumor infiltrated the surrounding tissues. One of his cases showed numbers of minute calcifications within a large malignant lesion of the breast. Salomon, however, did not draw any inferences from this case and it was not established until Leborgne, writing in 1951, was able to describe the type of calcifications found in breast cancer. He reported that about 30% of such lesions contained these tiny calcifications.

Since those times, other writers have described the association of benign breast disease with other types of mammary calcifications. The characteristic arterial calcifications and the extended linear calcifications of secretory disease are well known. They are easily differentiated from microcalcifications. Indeed, it is now possible in most cases to properly identify the nature of the lesion from the size, shape, location and number of the calcifications present. This is not to deny the diagnostic value of the appearance of a mass if present and, of course, the general architecture of the breast itself.

Several real problems in differentiating benign from malignant calcifications remain. Perhaps the most difficult problem in differentiation occurs in the similarity of calcific deposits seen in malignant disease but also present in adenosis and papillomatosis. All three of these conditions may be associated with minute calcifications and it is inevitable at this stage of our knowledge that the radiologist, even after a careful evaluation of all the factors, will have to list two or three of these conditions in a differential diagnosis.

There are, of course, diagnostic aids in the differential diagnosis. The thin rod-like forms seen in breast cancer, which Martin has described as thin linear, thin curvilinear and thin branching, do not occur in adenosis and papillomatosis but it is possible to see a malignancy in which rod calcifications are not present, only rounded forms being seen.

The rounded forms in adenosis and papillomatosis, however, are more sharply defined and more uniform in size than the malignant calcifications. By the same token a range of sizes and irregular borders point toward a diagnosis of malignancy.

While both forms of calcificatin tend to form clumps, the malignant calcifications are arranged in a more random fashion than the benign forms.

Fortunately, in adenosis, the distribution is usually bilateral and disseminated widely, a considerable aid in the differential diagnosis.

The presence of a mass with these calcifications, of course, weighs the diagnosis heavily toward malignancy.

The occurence of a small number of calcifications, perhaps under six, does not particularly differentiate between malignant and benign calcifications. It is common to find carcinoma with less. One has to choose between recommending biopsy or repeating the study after a suitable interval in doubtful cases. The value of an earlier baseline study for comparative purposes is illustrated by this situation.

Another area of interest in calcific differential diagnosis lies in the large irregular calcifications found in involuting fibroadenomas. Such a patient presents with a stony hard mass in the breast that may even be fixed and painless. The surgeon is certain of his diagnosis and may regard mammography as unimportant in these cases.

However, mammography will not only demonstrate the large, dramatic benign calcifications that the physician feels, it may also show a cancer lurking nearby. Furthermore, and especially in the dense, dysplastic breast, neighboring carcinomas may remain occult and the radiologist may counsel against surgery because of the characteristic calcific deposits. However, a recent survey has shown that an appreciable number of cancers will occur in such breasts and that one cannot advise against surgery only on the basis of the presence of the large calcifications.

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Nonvisualization of a Mass Lesion

A review of any large series of either screening or symptomatic mammograms will reveal the presence of interval cases, cases in which breast cancer is found within six months of mammograms read as negative. In the large breast screening centers this also means a negative physical examination of the breast.

Needless to say it is a most disturbing occurrence for the patient and the physician alike to have to deal with cancer within six months or so after this possibility was excluded. Some few of these may represent extremely rapidly growing cancers, not present at the time of the original examination but this must be a very small fraction of the total of interval cases.

Wolfe, Martin et al and personal experience indicate an irreducible margin of from 33% to 50% of these interval cases as truly not showing any roentgen sign on the original or pre-existing serial mammograms. This would represent from 4%–8% of all the cancers present. Within the framework of these figures, it is assumed that technique and positioning of the patient are up to a high standard of performance. A significant number of these false negative cases are small, dense breasts in which, in the absence of calcifications, a mass can easily be obscured.

Careful review of the remaining false negative cases does show evidence of error on the part of the radiologic interpretation. These errors include both oversight of direct signs of malignancy and lack of recognition of the more subtle indirect changes.

The single largest indirect sign in Martin's series is asymmetry. His group found that of the 18 interval cases that showed subtle and indirect changes rather than direct signs, 13 of these demonstrated asymmetry as the only sign suggesting neoplastic disease. If this asymmetry can be shown to increase in size or density on serial mammography, with or without a palpable mass, biopsy is a reasonable recommendation.

Decision Making

It is important for the radiologist to make a definite statement following his description report even though this may present a problem to the referring physician, especially the breast surgeon. For example a radiologic impression that calls for biopsy may place the surgeon who disagrees in a difficult situation, even invoking the specter of malpractice. However, the radiologist should back up his impression with what he thinks is the appropriate action for two basic reasons: the first is that he is showing confidence in his diagnosis and secondly because of his knowledge and experience in the various options that are available.

This particularly applies to a decision concerning cysts in the breast. For most surgeons, the nature of a palpable lesion must be determined whether by aspiration, biopsy or resection. Because of mammography, radiologists are seeing literally thousands of discrete breast lesions and are faced with decision making in each such case. Shall they follow the surgeon's example and recommend a definitive procedure in each and every case? Is that a practical solution? Can the radiologist be certain enough of the benign nature of a given lesion to reassure the referring physician and let a year pass before repeating the examination? Or should the interval be routinely set at six months or three months?

However difficult the problem the radiologist must produce a recommendation. For some radiologists the key to intervention is whether or not the lesion is palpable. It would seem that a decision reached that way is one to be made by the surgeon who primarily feels the mass. The characteristics of a benign cyst or calcified fibroadenoma are well-enough understood at this time to warrant a roentgen decision not to recommend surgery even though lesions like medullary carcinoma may very successfully mimic a clearly defined cyst. It goes without saying that solitary lesions, however well demarcated, need a careful follow-up, or in the presence of an increase in size, a surgical procedure.

The Scarred Breast

The breast that has been biopsied will frequently show skin thickening and variation in breast architecture as compared to the opposite breast. It is frequently impossible in the absence of previous studies to rule out existing carcinoma in such breasts. If previous films are not available for comparison this problem should be clearly stated in the diagnostic report and follow-up studies obtained. Once this skin thickening and other changes are established as stationary the case may revert to the yearly follow-up examination subject to the referring physician.

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Chronic Truncal Vagotomy: Its Effects on the Weight and Function of the Rat's Pancreas

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Introduction

The neurohormonal mechanisms that control basal pancreatic secretion in the rat have not yet been completely elucidated. Green (1, 2), Sarles (3–7), and Grossman (8–13) have suggested that CCK-PZ plays an important role in neurohormonal regulation but there is no general agreement as to the degree of neuronal participation, that is, cholinergic, in the control of basal secretion. However, fragmented data from the literature does suggest a definite role for cholinergic activity in secretion. For example, 1) it has been demonstrated that the vagi carry secretory fibers to the pancreas (14–16); 2) acute ligation of the bile duct inhibits basal pancreatic secretion by 30% (5); 3) ligation of the pylorus decreases protein, volume and bicarbonate output by 40% (17, 18), a reduction not related to endogenous secretin release. This latter depression of secretion was also observed in acute experiments in which section and reanastomosis of the duodenum was performed above and below the bile duct entry into the gut (19).

Concerning the secretory as well as the trophic changes induced by chronic truncal vagotomy in man and experimental animals, the literature is controversial (20–52). Discrepancy of results are due either to differences in species or to variations in experimental protocols used for the study of these parameters. With exception of the Petersen and Grossman report (10) on pancreatic secretion in nonanaesthetized rats after acute vagotomy, to our knowledge, no complete studies on basal bile-pancreatic secretion in conscious animals after long-term vagotomy have been reported. Moreover, it is not known whether the activity of choline acetylase, the enzyme responsible of the synthesis of the cholinergic neurotransmitter, acetylcholine, and which is located at nerve endings in the gland, is modified after vagal section. Finally, any chronic autonomic denervation of an organ is known to induce trophic changes, that is, atrophy, in the gland.

Therefore, the aim of our experiments was to analyze the following effects of chronic truncal vagotomy on the rat pancreas: 1) trophic changes, 2) basal secretion, and 3) choline acetylase activity in the pancreatic tissue.

Materials and Methods

The experiments were carried out in male Wistar rats with an initial body weight of 280–350 gm. Two series of animals were studied—a control group and an experimental group.

Control Group

In the first series, a biliary pancreatic fistula was created by modifying the technique described by Cavarzan et al (Fig. 1) (3). After entering the abdomen through a midline incision and under the dissecting microscope, a plastic catheter (diameter 0.65 in O.D.) was inserted in the terminal end of the bile duct. The distal segment of the duct was ligated with 6–0 silk and the catheter secured with another ligature of the same material. One of the main modification of Cavarzan's technique consisted of giving the draining catheter a hook form. The tip of the short segment of the hook was bevelled to facilitate its entrance into

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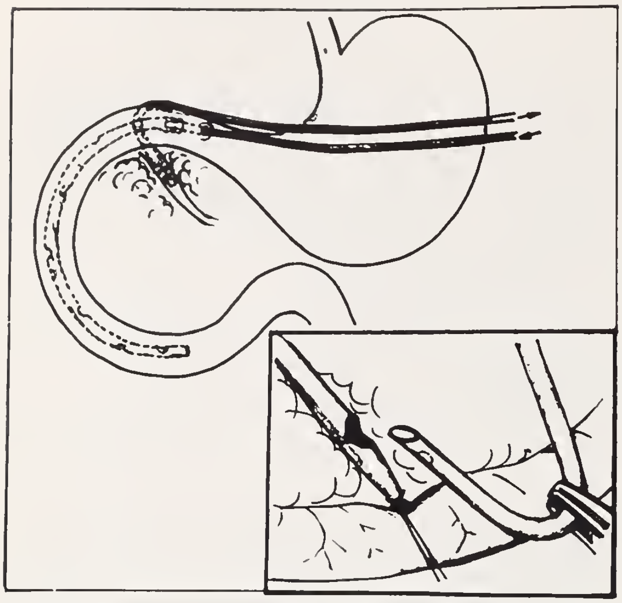

FIG. 1. Biliary pancreatic fistula.

the bile duct. Close to this tip, a small hole was made in the catheter opposite to the bevelled end. This was done to prevent interruption of the bile-pancreatic flow if movements of the plastic catheter caused opposition of its tip against the hepatic duct wall. The long segment of the hook was brought to the subcutaneous tissue at the left side of the midline laparotomy. Its course was from right to left crossing the abdominal cavity in a horizontal direction under the liver and in front of the anterior surface of the stomach. Prolonged by a silastic catheter, it was then brought to the neck through a subcutaneous tunnel. Another silastic catheter, 8 cm long, with several holes placed alternatively around its circumference, was inserted through a small incision in the posterior wall of the duodenum close to the pylorus. At this level, it was secured by a purse string suture. Prolonged by another plastic catheter (diameter 0.65 in O.D.) and after following a right to left course, it was brought to the subcutaneous level through the same incision previously performed at the left side of the midline laparotomy. From here, and through the subcutaneous tunnel, it was transferred to the neck. Marked elasticity of the silastic tube within the duodenum prevented deformation of the duodenal "C" form. This technical approach has two fundamental advantages. First, it permits unfolding of the mesoduodenum pancreas through which the bile duct courses. This permanent stretching of the mesoduodenum by the intraduodenal silastic tubing prevents its shrinkage and retraction and, thus, avoids impairment of bile flow and pancreatic drainage through the several small ducts tha enter the distal segment of the hepatic duct. Second, both the silastic intraduodenal tube inserte through the posterior wall of the first part of th duodenum and the modelling as a hook of th plastic catheter draining the bile duct allow normal positioning of the duodenum, a prerequisite to maintaining an unimpaired flow of the bile-pancreatic juice to the neck and its recirculation into the upper small bowel.

The surgical procedure was always performe during the morning hours, without previous fasting. Between tests, animals were kept in individual cages. Both catheters in the neck wer connected to each other to allow recirculation o bile-pancreatic juice into the gut. Rats wer tested during the first three days followin surgery. Experience has shown that during thi period the bile-pancreatic juice flow is regula and reproducible. During the first 48 hours, th animals were allowed to drink tap water but foo was withheld. After 48 hours, when the test o this day had been completed, the rats were allowed to eat. Animals were sacrificed and autopsied 48–72 hours after surgery.

Experimental Group

The second group of animals was subjected t truncal vagotomy plus pyloroplasty. The initia weight of this series of rats was similar to th controls. Without previous fasting, and unde ether anaesthesia, an upper midline laparotom was performed. After isolation of the esophagu and under the dissecting microscope, the thi branches of the anterior vagus nerve were transected. The posterior vagal branch was sectioned between two ligatures of 6–0 silk. The surgica procedure was completed with pyloroplasty Within 30 to 90 days, the rats were reoperate upon to create the biliary-pancreatic fistula as described for controls. As in the first series, functional evaluation was carried out within the initial 48 hours.

In both series of animals, testings were alway done during the morning hours, between 8 a.m and 11 a.m., at room temperature which oscillated between 25°–27°C. Rats were placed in Bollman cage (59). The tubes in the neck wer disconnected and the bile-pancreatic juice wa collected in small calibrated tubes immersed i crushed ice. The collection periods were 30 minutes each. Analysis was confined to the first thre periods (90 minutes) which showed steady levels The average values of the last two periods wer considered as the "plateau." The following parameters and methods were chosen for the biochemical assays: a) Volume (ml in 30 minutes) was measured with a precision of 0.1 ml, b) Bicarbonate concentration (HCO_3^- in mEql) was determined by the titrimetric method described by Lehmann et al (60), c) HCO_3^- output was calculated and was expressed as μEq/30 min, d) Protein concentration was measured according to the method described by Gornall et al (61), e) Protein output was expressed as mg/30 min, f) Lipase concentration was determined by the method described by Bang (62), modified by Lehmann (63), by converting the original technique to a titrimetic procedure, and g) Lipase output was expressed as U Bang-Lehmann/30 min.

After secretory studies, rats were sacrificed by a blow to the neck. The pancreatic gland was carefully dissected from the surrounding tissues and the head of the organ was isolated from the body and tail. The head is defined as the segment of the gland between the pylorus, the internal border of the duodenum and a line drawn along the right border of the mesenteric vein and passing through the pylorus. The remaining gland is considered body-tail. The dissection of the gland was done carefully, trying to remove all the fat tissue which surrounds the body-tail. The pancreatic tissue was blotted dry and weighed.

Enzyme activity was determined in an acetone dried powder of pancreatic tissue, according to the method described by McCaman and Hunt (64). The buffer substrate solution contained: 0.07 M potasium phosphate (pH 7.4), 0.3 M NaCl, 5×10^{-3} M choline, 2×10^{-4} M eserine, 2×10^{-2} $MgSO_4$, 0.05% bovine plasma albumin, 5×10^{-5} M (^{14}C) acetyl-CoA (^{14}C) with specific activity 60 mCi/mmole. The reaction was started by addition of 5 μl of acetone solution (equivalent to 250 μg of acetone powder), was carried out at 37°C for 30 minutes, and was stopped by the addition of 1 μl of 200 mM choline in 3 N trichloroacetic acid. The precipitated reinickated salt of (^{14}C)-acetylcholine formed after the addition of ammonium reinickate was washed with 0.5 N HCl, centrifuged, and dissolved in 100 μl of acetone. Aliquots of 20 μl were removed and added to counting vials. One milliliter of methanol and 10 ml of a toluene-scintillator solution (4 gm PPO and 0.1 gm POPOP/1 of toluene) were added to each vial. Radioactivity was determined in a scintillation counter system. Enzyme activity was calculated on the basis of the known specific activity of ^{14}C-acetyl-CoA and were expressed in μg. acetylcholine formed/hr/per head or body-tail (total activity) or in μg acetylcholine formed/hr/gm acetone powder (concentration).

For morphologic study, both the head and the body-tail of the pancreatic glands were fixed in neutral formol calcium. The following staining techniques were used: haematoxylin-eosine, Gomori, and Masson Trichrome.

Statistical analysis consisted of calculating the mean and standard error of the mean of the results. The significance of the differences between means was evaluated using the Student's t test for nonpaired values (65). P values less than 5% ($p < 0.05$) was interpreted as significant.

Results

1. *Gland Weight*

Within two to three months after truncal vagotomy, the wet weight of the whole pancreas markedly increased by nearly 103% (Table I). This increase in gland weight after vagotomy was highly significant ($p < 0.001$) and was observed in the head as well as in the body-tail. Thus, the trophic effect of vagotomy induced an 81.6 ± 10.43% increase in the weight of the head and a 101.81 ± 9.63% increase of the gland's body-tail weight, (n = 10) when compared with control values.

2. *Basal Secretory Activity*

The volumes (A), bicarbonate concentration (B) and bicarbonate output (C) values in controls and chronically vagotomized glands can be seen in Figure 2. In vagotomized rats, the volume secreted was slightly increased when compared with controls. It reached statistically significance levels ($p < 0.05$) at 60 and 90 minutes after starting the bile-pancreatic juice collection (60 min: from 0.80 ± 0.052 ml/30 min in controls, n = 13,

TABLE I

Weight of Pancreas, Head and Body and Tail in: 1) Controls and 2) Rats Subjected to Chronic Truncal Vagotomy and Pyloroplasty

Weight	Controls	Vagotomized
Whole Pancreas (mg)	953.2 ± 32.46 (n = 10)	1936.6 ± 92.18** (n = 13)
Head (mg)	347.1 ± 30.21 (n = 10)	621.6 ± 74.85* (n = 11)
Body and Tail (mg)	618.9 ± 31.33 (n = 10)	1314.1 ± 98.62** (n = 11)

Values are mean ± SEM.

* $P < 0.005$, when compared with control values.

** $P < 0.001$, when compared with control values.

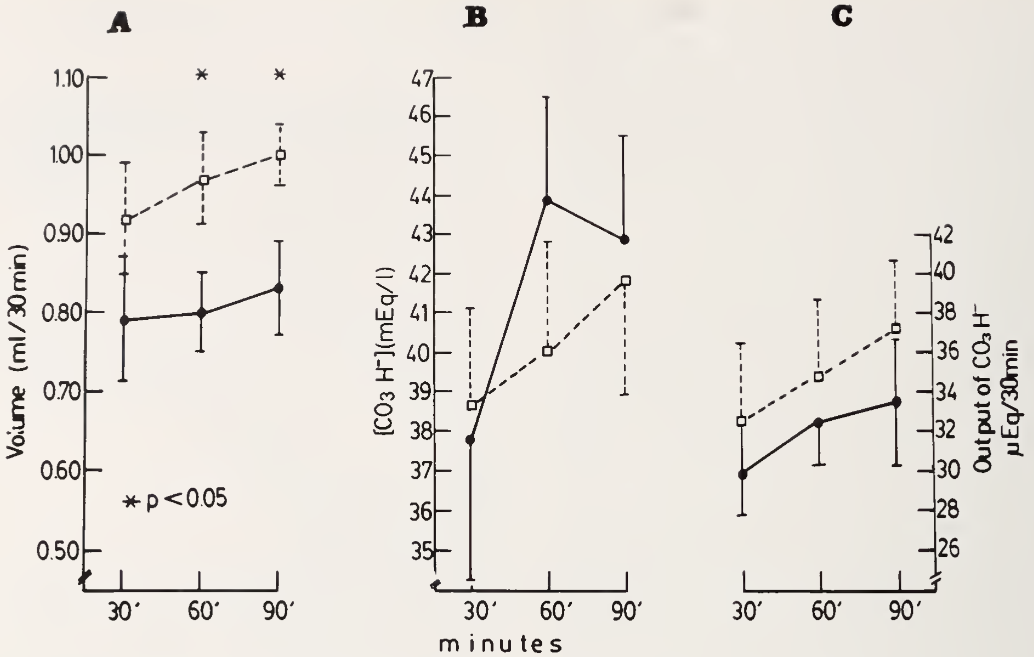

FIG. 2. Hydrelatic component of bile pancreatic juice from normal and chronic vagotomized rats. A: Volume secreted. Ordinate: volume (ml/30 min). B: Bicarbonate concentration. Ordinate: (HCO_3^-) mEq/1. C: Bicarbonate output. Ordinate: (μEq/30 min) Abscissa: time in minutes (30, 60 and 90′) ●——●: Controls (n = 13) (○----○: Vagotomized rats (n = 15) The values shown are mean ± S.E.M. *$p < 0.05$ when compared with control values

to 0.97 ± 0.063 ml/30 min in vagotomized rats, n = 15; 90 min.: from 0.83 ± 0.062 ml/30 min. in controls, n = 13, to 1.00 ± 0.041 ml./30 min., n = 15 in denervated glands).

Both bicarbonate concentration (Fig. 2B) as well as bicarbonate output (Fig. 2C) of chronically denervated glands did not differ in the three periods studied from those obtained in control glands.

During the first period of 30 minutes, the protein concentration from denervated glands (Fig. 3) was found to be 9.38 ± 0.925 mg/ml (n = 15), which was not different from the values of the controls (9.14 ± 0.651 mg/ml (n = 13). At the second and third periods, protein concentration in the bile pancreatic juice of denervated glands was decreased, although only in the former was the difference statistically significant, that is, from 11.79 ± 0.841 mg/ml (n = 13) in controls to 9.48 ± 0.694 mg/ml (n = 15) in denervated glands ($p < 0.05$). On the other hand, protein output was not influenced by chronic vagotomy (Fig. 3).

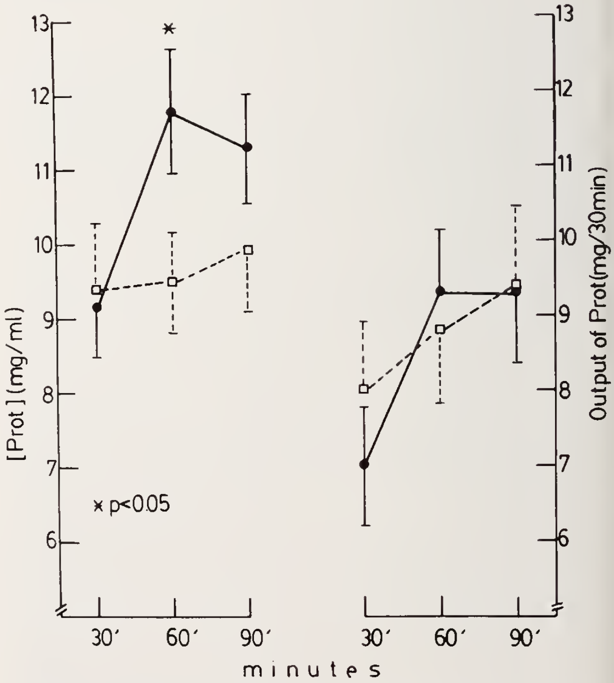

FIG. 3. Ecbolic component of bile pancreatic juice from normal (●——●) and chronic vagotomized glands (○-----○). To the left, protein concentration in mg/ml and to the right protein output in mg/30 min. Abscissa: Time in minutes (30, 60 and 90′). The values shown are means ± S.E.M. of 13 experiments (controls) and 15 (vagotomized). *$p < 0.05$ when compared with control values.

3. *Lipase*

Both lipase concentration as well as output were significantly decreased after chronic vagotomy (Fig. 4). The inhibition (about 60%–70%) was observed in the three periods studied, for

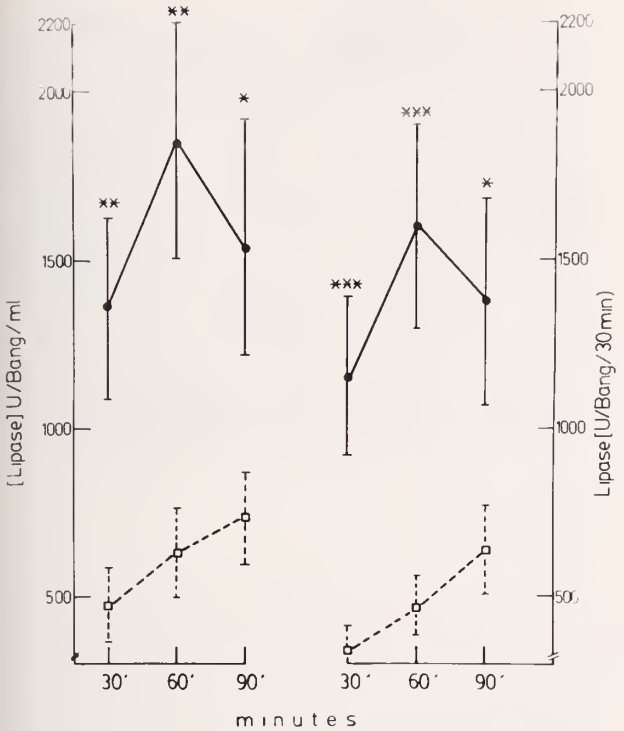

FIG. 4. Lipase in bile pancreatic juice of normal and chronic vagotomized animals. Ordinates: to the left, lipase concentration (U/Bang/ml); to the right, lipase output in U/Bang/30 min. Abscissae: time (minutes). Values were determined at 30, 60 and 90 minutes. ●——●: Controls (n = 10) □----□: Vagotomized (n = 14) Values are means ± S.E.M. n = number of observations. $^*p < 0.01$; $^{**}p < 0.005$; $^{***}p < 0.001$

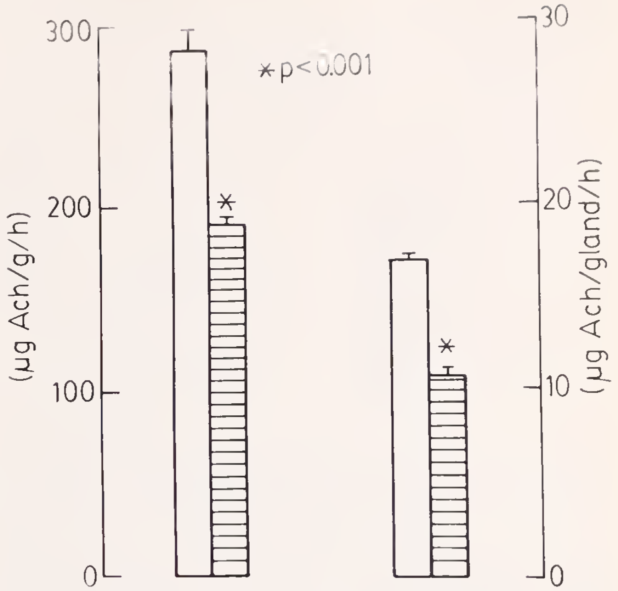

FIG. 5. Choline acetylase activity in the head (□) and body-tail (▤) from normally innervated pancreas. Ordinates: To the left, enzyme activity in µg Ach/gm/hr (concentration) and to the right, total enzyme activity in µg/Ach/head or body-tail (gland)/hr. The values shown are means ± S.E.M. of 8 experiments. $^*p < 0.001$

example, 30 min: lipase concentration: 1362 ± 271.4 in controls, (n = 10) to 472 ± 115.2 U Bang/ml in denervated rats (n = 14); 30 min lipase output: 1156 ± 235.6 in controls (n = 10) to 341 ± 64.7 U Bang/30 min in denervated rats (n = 13) ($p < 0.001$).

4. *Choline Acetylase (Ch Ac) Activity*

The pancreatic glands studied had measurable quantities of choline acetylase. Enzyme concentrations were determined in the head and in the body-tail of the glands. In controls, Ch Ac content varied considerably between these two structures. Indeed, the enzyme content of the head was significantly higher (by about 50%) than that obtained in the body-tail (Fig. 5). Thus, the average concentration of Ch Ac (Calculated per gm powder) in the head was 284.9 ± 10.58 µg Ach/gm/hr (n = 8) which was significantly higher ($p < 0.001$) than that of the body-tail, 190.7 ± 3.18 µg Ach/gm/hr (Fig. 5). The total ChAc activity (calculated per whole gland) was also significantly different ($p < 0.001$), for example, 17.3 ± 0.59 µg Ach/gl/hr in the head and 10.9 ± 0.52 µg Ach/gl hr in the body-tail (n = 8). When compared with their respective controls (Fig. 6), Ch Ac activity, calculated per whole head or whole body-tail, markedly decreased within two to three months after chronic vagotomy in both segments of the glands. The fall in total activity in the head was about 35%, from 16.4 ± 0.92 µg Ach/head/hr in controls (n = 8) to 9.9 ± 0.52 µg/Ach/head/hr. in parasympathetically decentralized glands (n = 6). This difference was significantly significant ($p < 0.001$). Similarly, the body-tail of the pancreas also showed a marked decrease (35%) in total enzyme activity after section of the vagal parasympathetic fibers (Fig. 6). The total activity of the denervated body-tail decreased to 6.8 ± 0.42 µg Ach/body-tail/hr. from 10.2 ± 0.82 µg/Ach/body-tail/hr in controls. These differences are significant ($p < 0.01$). The Ch Ac concentration of both, the head and body-tails of decentralized glands, were found to be also significantly inhibited by 33% and 15%, respectively, when related to control values. The head's choline acetylase concentration was 276.4 ± 8.90 µg Ach/gm/hr in controls (n = 9). After vagotomy (n = 6), it was reduced to 180.1 ± 6.45 µg Ach/gm/hr ($p < 0.001$). The enzyme concentration in the body-tails of controls, (183.4 ± 6.40 µg Ach/gm/hr) was decreased to 160.2 ± 7.30 µg Ach/gm/hr after the surgical procedure ($p < 0.05$) (Fig. 6).

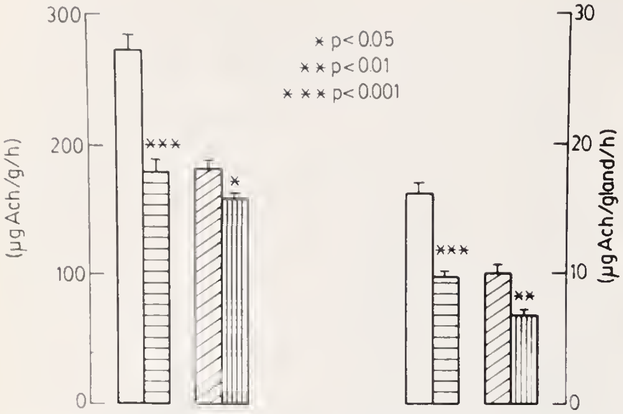

FIG. 6. Choline acetylase activity in the head and body-tail of normally innervated pancreas (controls) and in the head and body-tail of truncal chronic vagotomized rats. Ordinates: to the left, enzyme concentration in μg/gm/hr; to the right, total choline acetylase activity in μg/head or body-tail (gland)/hr. ☐ head of controls (n = 8) ▤ body-tail from controls (n = 9) ▨ head of vagotomized rats (n = 6) ▥ body-tail from vogotomized rats (n = 6). Values shown are mean ± S.E.M. n = number of observations.

5. *Morphology*

Histologic study of the pancreas of vagotomized rats revealed an increase in the size of the pancreatic lobules as well as in the gland's acini. In addition, there was proliferation of young acinar cells, characterized as small elongated, darkly staining and with a scarcity of secretory granules (Figs. 7, 8). Some lobules were formed exclusively of these cell types. Another striking observation was an apparent reduction of the ductular mass and of the Langerhan's islets.

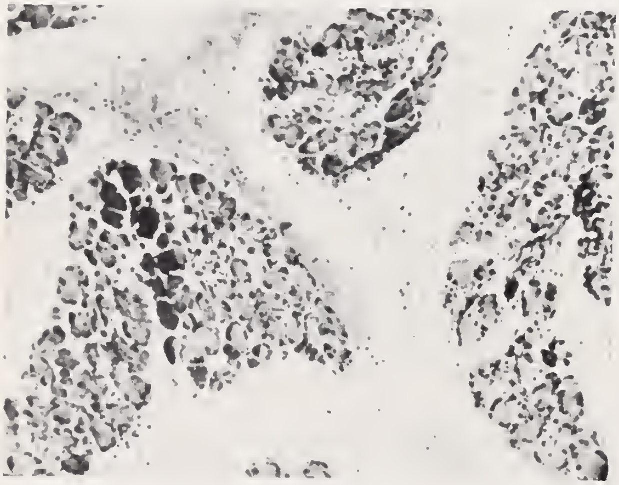

FIG. 7. Small, dark, round or polygonal acinar cells within pancreatic lobules (Hematoxylin-eosine; original magnification ×50).

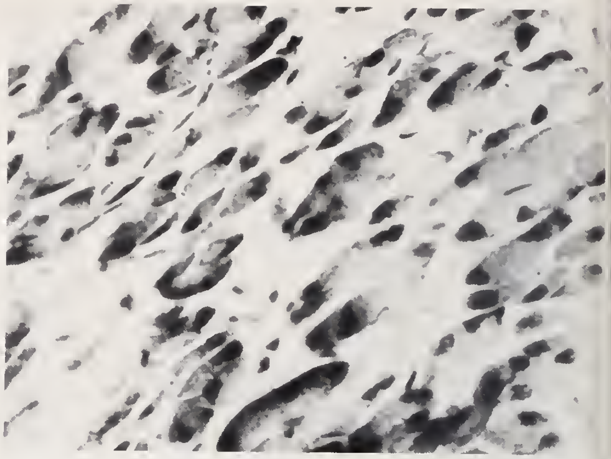

FIG. 8. Fusiforme cells, with their nucleus in polar position; the cytoplasm shows scanty secretion (Hematoxylin-eosine; original magnification ×150).

Discussion

The high levels of pancreatic choline acetylase activity obtained in this study confirm our previous histochemical observations in dogs (57) and are consistent with the rich cholinergic innervation of the rats' pancreas. While there are numerous reports concerning acetyl choline synthesis in tissues of the central and peripheral nervous systems of mamals (27, 34, 43, 46, 53), the present data presents additional evidence of its synthesis in the pancreas rates higher than in the parotid and submaxillary glands (77, 78). Indeed, acetyl choline activity varies considerably with the various organs of a species as well as in different species, for example, the rabbit and the dog have higher concentrations than the cat and the rat (54, 58).

The observation that the pancreatic head synthesizes more acetyl choline than the body-tail requires elucidation. This difference can, in part, be explained by a greater number of cholinergic nerve terminals in the former structure than in the latter, confirming macroscopic anatomic findings in man and dogs that show a greater density of nerve fibers in the head than in the body-tail of the gland (43, 45, 46). Vagisection, of course, abolishes nerve impulses from the central nervous system (56) through preganglionic fibers to their synapses with postganglionic fibers within the pancreas. A necessary consequence of this decreased tone would be decreased choline acetylase activity in the postganglionic fibers and pancreatic tissue. In accordance with these physiologic considerations, vagisection in the present study induced a decrease in choline acetylase activity in both the head as well as the body-tail of the pancreas. The decrease in activity as judged by concentration (per gm of gland or acetone powder) as well as total activity (per gm of structural region) was more marked in the head of the gland than in the body-tail. The degree of inhibition of choline acetylase activity ranged between 35% – 40% and is of the same magnitude as reported for other organs after preganglionic denervation but lower, as expected, to the decreased activity reported after postganglionic denervation (55, 56).

A number of mechanisms exerting trophic influences on the pancrease might explain the weight gain observed following vagisection. One possibility is gastrin, a hormone accepted trophic to the pancreas (12, 66). After chronic vagotomy, gastrin level rises (37, 47, 67) as a result of gastric acid secretion depression and interruption of inhibitory cholinergic fibers regulating the hormone's release from the gastric antrum. In the present series of experiments, serum gastrin levels were not determined. Another pancreatotrophic factor to be considered is CCK-PZ (12, 34, 68–71). Following vagisection, increased serum CCK-PZ levels have been reported in man (55). Dorchester found augmentation of intestinal mucosal activity following vagisection in the rat (25). Petersen et al (12), administering CCK-PZ subcutaneously to rats for 15 days reported pancreatic changes similar to those noted in the present experiments, that is a) an increase of 56.8% of pancretic gland weight over controls, b) an augmentation of the number of acinar cells and of the ratio acinar/ductular cells masses, c) a nonsignificant reduction in percentage of Langerhans islets.

Hypersensitivity of the intrapancreatic ganglia as a result of decentralization must also be considered. Catanzaro (52) observed this in rats given Scorpion Tityus Serrulatus toxin. Indeed, tests performed with this agent triggered a higher pancreatic amylase secretion in vagotomized animals than in controls. In general, the neurohormonal relationships in the intrapancreatic ganglions are complex and incompletely understood. Recently, V.I.P. substance P, enkephalins, gastrin, and CCK-PZ have been reported to be present in these situations (72). Presumably, vagal section could exert changes in the absolute amounts or relative proportions of these neurotransmitters within the intrapancreatic ganglion cells and, in this way, modify their influence on the "pancreon" (73) and Langerhans islet cells.

The late effects of vagisection on basal secretion, that is, a) the slight but significant increase in flow, and b) the slight but not statistically significant augmentation of bicarbonate output, can be explained by the following factors acting alone or combination: a) an increase of the pancreatic ductular mass, b) high CCK-PZ blood levels acting on young acinar cells, c) a facilitation of the potentiation that CCK-PZ normally exerts on the secretion of water and electrolytes by the hormones of the secretin family on the "pancreon's" centro-acinar-ductal segment (74), d) the removal of restraining influences normally exerted by vagal inhibitory fibers on the hydrelatic component of basal pancreatic secretion, e) the developing of "pancreon" hypersensitivity to hydrelatic agents, to secretin, or other members of its family acting on the ductular mass, or the CCK-PZ exerting its effects on the acinar cells, f) an increase of the nonbile salt dependent fraction of bile secretion.

The participation of the first factor (a)—an increase of the pancreatic ductular mass—is dubious. Actually, microscopic study of the vagotomized pancreas disclosed reduction of the ductular and islet masses. This observation is consistent with Petersen's findings following chronic parenteral administration of CCK-PZ to rats (12). The possibility (b) that the observed postvagotomy augmented flow could result from increased CCK-PZ levels acting on newly formed acinar cells is partially suggested by the data indicating a similar electrolyte secretion from the rat acinar cell (13). Possibility (c) is suggested by experimental data in dogs (29, 30). The hypothesis that chronic vagotomy could interrupt restraining influences normally exerted by vagal inhibitory fibers (d) on flow rate was primarily conceived by Tankel and Hollander (80). Even Claude Bernard presented evidence of vagal pancreatic inhibitory fibers. The possibility that the changes in basal secretion following chronic vagisection are related to hypersensitivity of the developing pancreon (e) would follow a linkage between pancreatic cell sensitivity and gastric acid secretion. Indeed, patients with low gastric acidity show greater sensitivity to exogenous secretin than patients with high gastric acid secretion (42, 79). Although gastric juice was not collected in these experiments, it is reasonable to assume decreased gastric acidity, hence increased ductal cell sensitivity, developed following the vagisection. The possibility that augmentation of bile flow (f) could have participated in the observed postvagotomy basal hypersecretion is supported by studies in dogs and monkey reported by Tanturi and Ivy (21). A final consideration as causal to the observed phenomenon of postvagotomy basal augmented pancreatic flow is the possibility that a ligature around the hepatic duct might interrupt nerve influences, besides those of the vagi, to the liver and to the pancreatic gland (5).

Reports of basal pancreatic secretory changes following vagotomy in other species are scarce. The dog has been the animal most frequently studied. Tankel and Hollander (80), Moreland and Johnson (81) have observed that vagi decentralization does not alter either flow rate or bicarbonate output. On the other hand, Konturek et al (36) and Debas et al (39), reported both these paramenters significantly decreased. In a study carried out in human subjects, Shingleton (cited by Tankel and Hollander (80)) found a five-fold increase of basal pancreatic flow after vagotomy. This interesting observation has been neither confirmed nor denied by further reports in the literature.

Chronic vagotomy induced changes in the ecbolic component of basal bile-pancreatic juice. Protein concentration was significantly decreased in respect to control at 60 and 90 minutes. Protein output, on the other hand, remained unchanged after vagal section. These findings are in agreement with those reported by Petersen and Grossman (10) in vagotomized rats, although in these experiments, the vagus section was performed only 48 hours before the test. This lack of effect of chronic vagotomy on rat basal protein secretion is in contradistinction with the findings in dogs. Indeed, Konturek et al (81), Debas et al (39), have reported a significant fall of basal protein output.

Undoubtedly, the most striking observation in the basal secretion of the vagotomized animals was the depression, both in concentration and output, of lipase. The percentage fall in respect to the control was 60% – 70%. If this finding is linked with the fact that cholinomimetics agents evoke a preferential release of this enzyme from the rabbit pancrease in vitro (75), one could tentatively infer that lipase is a cholinergic dependent enzyme. The marked inhibition of lipase secretion after chronic vagotomy in the present series of rats, also can be correlated with the report in man of a selective depression of this enzyme in duodenal contents following vagal section, either in the basal state or after endogenous and exogenous stimuli (38). It is also in agreement with the observation of a significative postprandial depression of lipase and bile acids in the jejunum, emphasized by Fields and Duthie (76) in vagotomized man, an observation which could explain post truncal vagotomy steatorrhea in man.

Summary

The effects of chronic truncal vagotomy on the pancreatic gland was studied in male adult Wistar rats. Two to three months after parasympathetic decentralization, the gland weight was found to be significantly increased by nearly 100%. This trophic effect is mainly due to the proliferation of young acinar cells. Concomitantly, there is a decrease of the ductular mass and of the Langerhans islets. Choline acetylase activity was decreased by about 35% – 40% in the vagotomized pancreas. Further, enzyme concentration was found to be greater in the head than in the body and tail of the gland, thus suggesting a higher nerve density of vagal cholinergic fibers in the former than in the latter. Basal pancreatic secretion of the decentralized glands showed a significant increase in the flow rate with no significant changes in both bicarbonate concentration and output. Protein concentration was significantly reduced at 60 minutes; protein output remained unchanged. The most remarkable finding was the fall in both lipase concentration and output (60% – 70%) when compared with control values. These findings may be related to clinical manifestations after long-term vagotomy.

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The Anatomy of Norman Cousins' Illness

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The December 23, 1976 issue of *The New England Journal of Medicine* published a special article by Norman Cousins "Anatomy of an Illness (As Perceived by the Patient)" (1). In it, the author described his recovery from a serious nonfatal, supposedly irreversible illness. Mr. Cousins agreed to submit the article because the story, which he had been relating in social conversation for several years, had already appeared in someone else's book. The author admitted that his was a single case, anecdotal in character; he did not insist that it be accepted as proof of anything. Unfortunately, the text contradicted his disavowal; generalized conclusions were drawn and personal theories and opinions about disease in general were presented.

The "anatomy" of Mr. Cousins' illness is an account based on a large number of hypotheses, each shaky in itself, combined to reach an unwarranted conclusion. We are told of a patient with a disease of unknown cause and of uncertain nature, who is sure his illness was caused by a combination of fatigue, street fumes he inhaled in his hotel room, and the heavy metals he inhaled from an airplane exhaust. He cured himself by laughter, vitamin C and self-will. The points the patient has plucked from his history are linked into a continuum of conjecture, supported by facts culled from the scientific literature and extrapolated beyond reason. Data that do not fit are ignored.

In 1979, the article was reprinted and the material expanded into a short book by the inclusion of several essays on somewhat related subjects (2). As of September 1980, it had been on *The New York Times* best-seller list for one year. Cousins modestly characterizes his report as "an account" but a man of his sophistication must know how authoritative his voice is, how deservedly important he himself is, that people will take him at more than his literal word. His disavowal of the general application of the advice he gives must then be disingenuous. Although the book is not antiscientist or antidoctor, it is prointuition, and pro a semimystical credo, clothed in scientific terminology.

It is understandable that the promotional material and the bibliography fail to mention that Dr. F. J. Ingelfinger, the editor of *The New England Journal of Medicine,* in an editorial in the same issue in which the original article appeared, says "The history of illness is replete with cures in the face of rash medical predictions of death. All experienced physicians are sensitive to the remarkable influence of the patient's attitude" (3). The full editorial is a devastating criticism of the Cousins article. Dr. Ingelfinger makes one important error, however, an error common to many readers of this book. He assumes Cousins had an illness that endangered his life although Cousins nowhere actually says so.

I find it distasteful to criticize this particular author. I know Norman Cousins, like him and admire him. He has had a distinguished career. He is a man of superior character and intelligence, an active participant in issues of major ethical concern. He thinks and acts effectively on a global scale. His leadership of organizations dedicated to the pursuance of a sane nuclear policy, to international understanding and cooperation, his valuable initiation and leadership of humanitarian projects, all indicate his value. That is why I am distressed to see him add his influential voice to the growing army of "experts" on subjects far from their areas of expertise or understanding.

The Argument

The reprinted article, which constitutes the opening chapter of Mr. Cousins' book, is his story

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of a sickness he suffered in 1964. His theory, which he treats as a certainty as the book progresses, is that a frustrating and debilitating week in Russia caused exhaustion of his adrenal glands. This left him susceptible to pollutants (hydrocarbons and heavy metals) from the exhaust of diesel trucks that passed beneath his open second-story hotel window during the week, and from the spew of a jet plane exhaust that he inhaled at the airport at the end of the week. He felt ill on the plane returning from Moscow. He soon developed fever, body aches, and very painful stiffness of most of his body, severely limiting motion. He was hospitalized, seen by many consultants, and was given several medications which not only did not help but did damage. Recovery from the illness was finally brought about by a regime of body-shaking laughter and the administration of extremely high doses of vitamin C, potentiated by the patient's "well-developed will to live." The treatment was carried out "in partnership" with his physician (whom I know to be a very good one).

The efficacy of the treatment was proven, Cousins claims, first, by the statement attributed to one of his consultants that he had never seen anyone recover from this illness, and second, by the fact that his erythrocyte sedimentation rate dropped after each episode of laughter and after each injection of vitamin C. The book's many contradictions and its complex mélange of fact and fancy make it difficult to grapple with. On some pages vitamin C is a medicine, on others it may be a nonspecific placebo. The scientific method is described and approved, then flouted.

Cousins defends the physician's reluctance to practice an unproved therapy "in the absence of adequate clinical evidence that it is safe and efficacious." And again: "I would not want to take the responsibility for advising anyone who is seriously ill to forego the soundest medical advice obtainable." But it is the patient, according to the argument in this book, who decides whether that advice is "the soundest" and what is "efficacious."

Several readers (probably very many) believed that Cousins' self-prescribed treatment saved his life. His doctor "admitted that one of the specialists had told him I had one chance in five hundred, that he had not personally witnessed a recovery from this comprehensive condition." A reader who has not paid close attention may conclude, in error, that the specialist was referring to survival, not to recovery from the disease. As we have seen, the editor of the periodical that printed the original article made this mistake. A 1980 interview with Cousins was introduced thus: "*Anatomy of an Illness* tells the extraordinary story of his recovery from an ailment that had seemed fatal" (4). Mr. Cousins does not say that his disease was expected to be fatal. Nevertheless, his juxtaposition of the description of his illness and its outcome, "the pronouncement of doom" he says he received, his repeated references to his "will to live," and statements that people can be "programmed to die and programmed to live" are obviously misleading. "Will to recover" would be a more accurate phrase than "will to live" in the context of this case report, although admittedly less dramatic.

Although I do have reservations and, in some areas, strong objections to what Cousins writes, my disagreement by no means extends to all of the text. He is a thoughtful man. His discussion of some general topics is valuable. He writes of the role of nutrition in health and disease, the responses of the body to pain, the danger of overmedication (too often initiated by the physician). He stresses the need to get more physicians into family (rural and urban) practice. He emphasizes the value of a physician-patient cooperative effort in management of disease. The specialist may be so busy doctoring that he has no time to be a doctor. Being reminded of that should do us physicians good. The patient deserves the doctor's ear, his time, his compassionate hand. But I do not know if doctors who are not naturally inclined to give of themselves can be taught to simulate concern. If the physician mimes a sincerity he does not naturally feel, the patient is likely to sense the artifice and be frightened by it.

After publication of the original article many doctors wrote to the author. To his surprise he learned that physicians are often not as unaware of their patients' emotional needs or as mechanically impersonal as he had apparently thought they almost always were. This surprise comes a little late in his career. The 3000 physicians whose notes so encouraged him did not suddenly become sensitive. They were functioning in that way all along, but Mr. Cousins fortunately had little cause to make their acquaintance.

Mr. Cousins exhorts medical scientists to increase their efforts to understand the phenomena of the auto-immune diseases, from one of which he suffered. No one can fault such a nonspecific admonition. We must also make increased effort to study environmental and viral causes of cancer, the reciprocal mechanism between host and infecting agents, psychoses, congenital malformations. There is no need to lengthen this list. I defy anyone to come up with any aspect of the human condition that does *not* merit more attention than it is getting. Cousins says that medical students should spend more time in the study of the humanities. How can anyone deny it? Unfortunately specialists have just so much time to learn the fundamentals of their own discipline. Mathematicians do not get enough courses in history. Historians do not get enough courses in astronomy. Fully rounded men are assets, but they are few. The Renaissance man is now five hundred years old and mumbles a lot.

Cousins expresses legitimate dissatisfaction with hospital and medical routines—their exhausting, uncoordinated interruptions of the patient's day—and the depersonalizing effects of electronic aids in intensive-care units. The patient in such a unit, Cousins says, lacks "the sense of security and ease that the body needs even more than clicking surveillance." He does not mention, however, that the purpose of such units is to save lives. And they *do*. Many people are alive today who would almost certainly be dead if such units and their impersonal equipment did not exist.

One chapter summarizes present knowledge of placebos. In some patients the placebo seems to prompt a beneficial reaction in the body, often just as efficacious as that produced by the pharmacologically active drug. This is the "placebo effect," notably common in the perception of pain, and in diseases subject to suggestion or associated with the emotions. The placebo effect reemphasizes that soma and psyche have reciprocal influences and indeed have a single identity. Mr. Cousins admits that he may have been the beneficiary of this effect, that it may account for his recovery. "The mind can carry out its difficult and woundrous mission unprompted by little pills."

Cousins defends the physician against the public's impatience with the medical profession and its unjustified expectation of miracle cures. A scientist is handicapped because he is unable to say that he knows with absolute certainty that a hypothesis is true, a hesitancy not binding on the nonscientific theorizer. Some part of the general dislike of scientists may be a reaction to a very unpleasant trait their work forces them to assume, medical conservatism and a wariness of experimental data and scientific dicta.

Cause of the Disease

Cousins is sure that he knows what caused his illness. He presents a fetching but far-fetched story. Supporting data are largely illusory.

His physician "said that [the disease] could have come from any one of a number of causes. It could have come, for example, from heavy metal poisoning; or it could have been the after effect of a streptococcal infection." (The latter thesis is not mentioned again.) This is escalated to "My doctor theorized that the condition might have been caused by heavy-metal poisoning," and even to "the speculations of the doctors concerning heavy-metal poisoning." (It would be instructive to know whether the heavy-metal conjecture was introduced by his doctor or was a response to a direct query by his patient.)

At any rate, Cousins favors the heavy-metal theory and finds retrospective corroboration. He is certain he was poisoned both by the exhaust from diesel trucks passing outside his open window in Moscow and from the spew of large jet planes at the airport. He is convinced that he inhaled these fumes when he was "wrung out" and suffering from "exhaustion of his adrenal glands," a condition brought on by a semiofficial mission to Russia, "an exercise in almost total frustration." This suggests many questions. Have other people who slept in that hotel room gotten the same illness, or any illness? Some of them too must have gone to bed frustrated and exhausted. Did Cousins in fact inhale heavy metals in abnormal quantities? Did he show any evidence of heavy metal poisoning? Were any tests carried out to determine the presence of excessive heavy metal in his body? Is there any evidence anyway that collagen disease syndromes are caused by heavy metals?

Why was Mr. Cousins alone made ill? "There were two possible explanations," he writes, "one had to do with individual allergy, the second was that I could have been in a condition of adrenal exhaustion." Again, Mr. Cousins chooses to ignore the first thesis. He prefers its alternate. (It complicates matters too much to point out that there are, in any case, many more than these two possibilities.) "Assuming this [latter] hypothesis was true [of which he was 'increasingly convinced'] I had to get my adrenal glands functioning properly again." Was adrenal exhaustion diagnosed? Was a corticosteroid administered to replace the absent "adrenal gland secretion?" I hope not, because stress does not produce adrenal insufficiency, much less adrenal exhaustion.

There is a relation between stress and illness. It continues to be under study in several centers. Dr. Hans Selye has expanded the concept of biologic stress to include the body's reaction to any trauma. Yet most investigators are undecided on just what stress is. It may be related to personality, genetic traits, psychologic, sociologic, and environmental influences, circumstances of employment, family relationships. It is not known whether stress causes disease, aggravates or alters the course of a disease already incipient, or merely makes one more susceptible to disease-causing agents. Not much is known of the mechanisms involved—certainly not enough to conclude, as Cousins has, that its effect can be overcome by Vitamin C and laughter.

Cousins supports many of his hypotheses with quotations from scientific literature, none of which appears to me to be directly applicable to the case he builds. As a man crossing a stream will step only on those stones that lead him to the other side, so Cousins selects data that support his argument and ignores those that might discredit it. I wish scientific conclusions could be reached so straightforwardly. Had he chosen another interpretation of events during the week prior to the onset of his symptoms, I am sure he could have achieved an antithetical conclusion. This gambit may be and has been used to support any preselected hypothesis. It will not surprise anyone who reads the scientific and pseudoscientific literature to see how the strategy of intuition, guesswork, and selective quotations can "prove," à la Velikovsky, that the geologic history of the world is based on cataclysms; that, à la von Däniken, our world is peopled by the progeny of primitive peoples who mated with visitors from outer space; that Jack Ruby was part of a cabal to murder Kennedy and his murderer; that Shakespeare's plays were written by Marlowe or Bacon or Essex or even George Bernard Shaw. Mr. Cousins' edifice may be built of heavy metal but it stands on quicksand.

Diagnosis and Prognosis

Mr. Cousins' physicians had difficulty diagnosing his disease. This is understandable. Several of his symptoms were not consistent with the final diagnosis of ankylosing spondylitis. Onset of this infirmity is rare after the age of thirty. Subcutaneous nodules, which Cousins had, do not occur in ankylosing spondylitis. It is one of the collagen illnesses, a syndrome with a very wide variation in its manifestations and severity. Remissions do occur, and some patients are cured, although residual disability, particularly stiffness or fixation of the joints, is common. Death is not. However, since we are given none of the clinical reports or laboratory findings, we must take it that the disease was ankylosing spondylitis.

Mr. Cousins' doctor said that *one* specialist told him "[Cousins] had one chance in five hundred" for "*full* recovery." (author's italics). Later Cousins says the "specialists" told him that his condition was "progressive and incurable"; and again " . . . the consultants said." (Note the plural on repetition.) This intelligent and perceptive layman stoops to the identification of his specialist consultants as "the experts associated with Howard Rusk." What does that imply? As I do not believe in guilt by association, I do not believe in virtue by association.

Who was the consultant who had never seen a recovery and who gave the patient one chance in five hundred for recovery? What is his version of the prognosis he is said to have given? Was he quoted correctly? It would be interesting to solicit from him a retrospective analysis of his original diagnosis and prognosis now that he is supposed to have been proven wrong. Although Cousins pluralizes and quotes this consultant repeatedly, and uses him both as proof of the accuracy of the diagnosis and of the inevitable deterioration that was to be anticipated in the disease process, it is ironic to consider that, if he said what he is reported to have said, his gloomy prognosis seems to have had some validity. I hope it is not unkind to point out that Mr. Cousins, according to his own evidence, is almost entirely but not fully recovered.

Treatment

Mr. Cousins found that he was hypersensitive to his medication, that the aspirin, phenylbutazone, codeine, and sleeping pills were toxic "by allergy tests." I would like to see documentation of these "tests." (In most cases you can prove allergy to a medicine only by taking a little of it.) "I was hypersensitive to virtually all the medications I was receiving . . . no wonder I had hives all over my body." Is it conceivable that a physician would not discontinue medication at the first evidence of a hypersensitivity reaction, the most common of which is a rash, particularly if that patient were to tell him "I felt as though my skin was being chewed off by millions of ants?"

Laughter

Mr. Cousins had his doctor stop all medications and institute a regimen that was basically the self-administration of laughter, augmented by the intravenous intake of vitamin C. He says that hard, body-shaking laughter was a major factor in his recovery. The laughter was provoked by humorous literature, Marx Brothers movies, and the television show "Candid Camera." It is important, apparently, that the laughter be very loud, loud enough to disturb patients in adjacent hospital rooms. Mr. Cousins was induced to move to a hotel. (Hotel residents, it seems, are more tolerant.) If not boisterous, the laughter does not have the beneficial effects on blood chemistry that are essential for therapeutic purposes. It is an enchanting theory. If you have *joie de vivre,* you will ensure yourself a longer life in which to experience that joy. It is poetic, but reality is prosaic.

Some people, Cousins says, find that uncontrollable laughter "leaves the individual relaxed almost to the point of an open sprawl." Yet people who have spells of weeping to exhaustion often describe this same after sense of relaxation and cleansing calm. It is a common observation that weeping, when appropriate for the occasion, relieves tension. And, we are told, so does aggressive behavior—screaming or any other emotional outburst. The sensation Mr. Cousins describes after laughter is not unique for laughter.

The Erythrocyte Sedimenation Rate

Laughter, Cousins says, demonstrated "the ability . . . to reduce the inflammation of my joints, confirmed by a reduction in the sedimentation rate, both sustained and cumulative." Cousins quotes two medical authors, B. Ecanow and B. H. Gold, who wrote that "ascorbate [vitamin C] has a dispersal effect on clusters of red blood cells"(5). If this is true, if vitamin C has a direct effect on the ESR, that test then becomes useless as an index of the course of the underlying disease in a patient who is taking vitamin C, as Cousins was. Mr. Cousins laughed daily. The ESR went down daily. Therefore, laughter lowers the ESR. This syllogism is repeated several times. Cousins says that its validity is proven since the ESR did not rise between the self-administered therapeutic sessions. Since the ESR dropped not only after laughter but also after intravenous administration of 10-25 grams of vitamin C, one must ask whether or not it might not have dropped if the patient had cried instead of laughed, or taken large intravenous doses of substance X.

As a matter of fact, if the ESR had risen after each fall, and then fallen again after the next dose of laughter and vitamin C, the evidence might be more worthy of consideration. As it is, is it not more likely that if the falling ESR shows anything at all, it is that the patient was getting better without regard to the therapy? Cousins does say repeatedly that most diseases are self-limited. Why not this one? The fact that one of his many physicians said it was not to be expected does not seem to me to constitute the overwhelming proof of the diagnosis and prognosis that Cousins thinks it does.

He writes, "If laughter did in fact have a salutary effect on the body's chemistry, it seemed at least theoretically likely it would enhance the system's ability to fight inflammation." This is a speculation when first introduced; it is treated as fact on repetition. "The ascorbic acid was working. So was laughter. The combination was cutting heavily into whatever poison was attacking my connective tissue." "The connective tissue in my spine and joints was regenerating." One need not be a logician to understand that this escalation of symptoms into anatomic or physiologic equivalents is guesswork, a ridiculous leap from the known to the unknown. In scientific thinking, it is mandatory to ask that a belief lend itself to some sort of verification—some corroborative evidence more substantial than "I did thus and so and I got better."

Vitamin C

Cousins received a daily dose of 25 grams of vitamin C by vein. (Why did he stop at 25? Why not 50, a dose Dr. Linus Pauling has recommended for patients with cancer? One is just as logical as the other.) He chose the unorthodox intravenous route for its administration because he believed he could get his body to use more that way. He says, "Was there a coefficient of time in the utilization of ascorbic acid? . . . it seemed to me that the body would excrete a large quantity of the vitamin because it couldn't metabolize it fast enough. I wondered whether a better procedure . . . would be to administer [it] through . . . intravenous drip." Any one of those guesses could have been verified by simple laboratory tests. Instead, they are integrated into the author's dogma without further question.

"Was it possible, I asked myself, that ascorbic acid had a vital role to play in 'feeding' the adrenal glands? I had read in the medical press that vitamin C helps to oxygenate the blood. If inadequate or impaired oxygenation was a factor in collagen breakdown, couldn't this circumstance have been another argument for ascorbic acid?" These musings might be legitimate prologues to serious scientific study if the evidence were not so contrived. The implications that vitamin C is a medicine, and helps individuals whose body vitamin C is not depleted, and that it increases blood oxygenation above normal in normal people, have no supporting evidence. Cousins cites research "showing that ascorbic acid is essential for the [ultimate] synthesis of collagen." (This is one of the best known facts in medicine.) "The significance of ascorbate in the treatment of collagen diseases such as arthritis, therefore, seems compelling." The conclusion is illogical, much less compelling, unless it were shown that the collagen damage in these diseases is caused by a lack of vitamin C (which it is not) or that vitamin C is effective in arthritis (which it is not).

Vitamin C seems to be pushing vitamin E for preeminence as a panacea, although phenylhydantoin (Dilantin), colchicine, and dimethylsulfoxide (DMSO) are coming up fast. Not only is vitamin C promoted as an antidote to water pollution, air pollution and congestion; it replaces antibiotics for the prophylaxis of postoperative infection. Cousins writes, "with respect . . . to an environment becoming increasingly burdened with air and water pollution, congestion, noise, and stress, the antitoxic role of ascorbic acid cannot be overestimated." Yes, it can be, and it has been. The irony of Cousins' previous strong indictment of nostrums is that he is proselytizing for another. He recommends vitamin C for all connective tissue and stress diseases, refers to Linus Pauling for his advocacy of vitamin C in the treatment of viral disease, and E. Cameron and I. Stone for its effect on neoplastic disease. The adherents of the case for vitamin C as a medicine have got the field pretty well covered.

Dogmatists have an advantage over scientists. They can say with certainty that vitamin C helps cure whatever disease they say it cures. The scientist has only the weak response "There's no clear evidence that it does." Which of the two statements do you think will generate a headline or sell a book?

Aspirin

Just as I found it confusing to try to separate from each other the claims made for laughter and vitamin C, I also had a problem with the linked discussion of vitamin C and aspirin. "Facts" are presented to support the case for the benefits of the vitamin and the deleterious effects of aspirin in arthritis; on examination they prove insubstantial.

"The steady use of aspirin can be bad for patients with arthritis." Although Cousins hedges by using the words "steady" and "can," the sense of the passage from which that sentence is abstracted is that vitamin C is better than aspirin for arthritis. Any physician who has treated patients with arthritis knows that pronouncement is wrong.

His statement, at first a speculation that aspirin may be "actually harmful in the treatment of collagen disease such as arthritis" (a speculation with a very attenuated thread of evidence), becomes after a while a certainty, supported only by his repetition. No longer is it possible that aspirin "may be harmful to some patients", but it *is* harmful, and what's more, vitamin C is better. "Could it be," I asked myself, "that aspirin, so universally accepted for so many years, was actually harmful in the treatment of collagen illnesses?" The answer is no, except in those very few patients who have a bleeding tendency or who are sensitive to aspirin. "A single aspirin tablet can cause internal bleeding." Although true, this is a wild exaggeration.

The Nature and Abuse of Scientific Evidence

From a profusion of guesses, influences, suppositions, hypotheses, possibilities, speculations, Cousins, by idiosyncratic alignment and juxtaposition, has chosen allergy, adrenal exhaustion, red blood cell clumping, placebo effect, endorphins, vitamin C, cell oxidation, unknown biochemical effects of the pituitary stimulated by mental processes, and so on to erect a structure that is only one of the several score he could have created just as easily and with equal validity from the same building blocks. Dr. Ingelfinger, in the editorial in *The New England Journal of Medicine* alluded to above, says of Mr. Cousins' method of reasoning, " . . . the hypotheses that can be constructed are limitless."

We enter the realm of scientism, the use of scientific terminology and data for unscientific purposes, the artificial and arbitrary linear linkage of scientific material to support unjustified conclusions. This realm is almost impregnable because it is nearly impossible to prove something is *not* so. If a man believes in UFOs, ghosts, the deadly Bermuda Triangle, the power of the occult orgone, or reincarnation, there is no way of proving the opposite to his satisfaction. Any claim of a miracle should be subjected to the same critical examination as that required for canonization. Because of the highly suspect conclusions of this case, an investigation of the hospital and other medical records, interviews with all the attending physicians and consultants, and questioning of other official and unofficial envoys who have spent frustrating weeks in Russia and roomed on the second floor of that hotel, seem minimal requisites.

Many scientific "facts" are merely opinions clothed in fancy terminology. That is why research must be repeated, findings corroborated, and results reproduced by other investigators. Even the best thought-out and worked-out conclusions must be subjected to the laws of statistics to determine whether the probability of the conclusion is significantly different from one obtained by chance. This process is a strict master. Failure to follow it meticulously invalidates many medical "facts" that seem so obvious as to be thought axiomatic. In even a well-conducted scientific experiment the unconscious urge to legitimize a desired conclusion can warp the experimenter's judgment and distort even his reading of observations made by a machine. Every conclusion should be suspect. This is a source of disparagement of scientists, but "a public that is understandably impatient with the almost endless scientific process," as Cousins says, is well served in the long run by such medical conservatism. It has, for instance, taken twenty years to disprove the proposition that hard water protects against heart disease.

Mr. Cousins acknowledges this. He himself gives an excellent definition of the scientific method: "a way of thinking systematically, a way of assembling evidence and appraising it, a way of conducting experiments so as to predict accurately what will happen under given circumstances, a way of finding the fallacies in long-held ideas." Unfortunately, he gives it only lip service.

Cousins lives in a comfortable world, where everything fits. It is a rare therapy, no matter how outlandish, for which some relevant supportive report cannot be located in the literature. But in his extensive reading of the medical literature, did Cousins not come across any evidence contradicting his beliefs which was worth mentioning? In medicine, as in any other dynamic discipline, it is not enough to present "on the one hand" without acknowledging the evidence for "but on the other hand."

The fact that one or more medical authorities can be quoted as upholding a view is not conclusive. In recent history, proof that legionnaires' disease is caused by a specific microbe, *Legionella pneumophilia,* was a triumph of investigative medicine. Yet after the first recognized epidemic in 1976 in a Philadelphia hotel, many bizarre suggestions poured in from professional and lay "experts." A doctor in Pennsylvania said the disease was caused by nickel carbonyl, a poisonous industrial chemical; he found fatal levels of the toxin in the tissues of the victims, but not in control samples. Scores of suggestions for treatment were received. Among them was vitamin C. Like examples in medical history are legion.

Diseases of unknown origin are at one time or another attributed to every agent known to activate disease. Among such diseases are chronic degenerative conditions of the nervous system. Multiple sclerosis is an example. It has been attributed to, among other things, avitaminosis, the ingestion of toxic chemicals, infection by a virus, hereditary taint, cellular autoimmune reaction, or to combinations of several of the above. Each has been cited to support the case for one treatment or another. A patient who has had only one bout of multiple sclerosis with full remission could easily build a case for any one of the causes or treatments, and quote authoritative articles chosen from the medical literature in support.

The wide complex of diseases which have in common involvement of joints undergo so many apparently spontaneous remissions and exacerbations, and respond to so many therapies, many of which include a strong element of suggestion, that they illustrate par excellence the fallibility of "successful" therapies that "make sense." Unfortunately, many things that seem to make sense do not. "Making sense" is not enough. You have to have evidence. Choosing isolated and preselected data from the days prior to falling ill, and from the literature, is not evidence—not scientific evidence, at any rate. We are told Dr. Hans Selye "detailed the negative effects of the negative emotions on body chemistry." Cousins speculates, "If negative emotions produce negative chemical changes in the body, wouldn't the positive emotions produce positive chemical changes?" Any scientist or logician would realize how wide a gulf separates those two quotations, even though the author feels that one follows the other. Or again, "I remember reading that [depression] could produce harmful chemicals in the body, so it occurred to me that it's axiomatic that laughter would produce helpful chemicals." Here Cousins takes a leap from a hypothesis to axiom. I cannot believe that he, an editor and teacher, can possibly think that that is an axiom, or even that his second clause follows logically from the first.

I looked up a good number of references in the book's bibliography. All had nothing to do with Cousins' thesis or were misinterpreted. The reckless use of scientific terminology and the citing of irrelevant references to substantiate arbitrary beliefs constitute pseudoscience. One example will suffice: Cousins quotes the work of a team of investigators who "showed that ascorbic acid is essential for the proper functioning of prolyl hydroxylase, which in turn is essential for the synthesis of collagen. The significance of ascorbate [vitamin C] in the treatment of collagen diseases such as arthritis, therefore, seems compelling"(6). No, it does not. Suggestive perhaps, but by no means compelling. (The article cited is actually an inconclusive study on the possible use of L3,4-dehydroproline to prevent excessive deposits of collagen.)

In the chapter on holistic health and healing I find: "The biochemical manifestations of mental powers are being well-documented. Competent observers have written about yogis in India, for example, who were trained to slow down their pulse . . . or who can order their skin to resist burning. I myself have witnessed such demonstrations in India, so I know them to be true." I am afraid he does not. He saw yogis who walked on hot coals without burning their soles, and yogis whose pulse was slowed to a few beats per minute; he does not know that these are "biochemical manifestations of mental processes."

"I recognize that many people believe that astrology is a valid guide to treatment of serious illness. I respect their right to that opinion," He is more tolerant than I. Astrology is a pseudoscience that has been discredited by every investigation. If people can claim our "respect" for surrendering their wills to the control of astrology, why not respect all antirational cults, any of which can produce supporting testimonials by the hundreds? This is not to say that Cousins himself endorses any of those cultist barnacles which have attached themselves to holistic medicine.

Cousins says there are "cancer sufferers who, according to documented accounts, have recovered after taking Laetrile." "After" is the escape word. Mr. Cousins did not say "*because* they took Laetrile," although he does believe the Laetrile stimulated a placebo effect which cured these patients. (Incidentally, Ernst Krebs and his son, the folks who brought us Laetrile, are also the discoverers and promoters of pangamic acid, the great what-is-it of the "health food" crowd.) Spontaneous disappearance of untreated cancer does occur. Less well known to the laity, however, is the fact that the diagnosis of cancer is not always clear. Every busy surgeon has several cases a year in which the pathologist who examines a biopsy or even a full specimen cannot make up his mind. When this specimen is then submitted to consultant pathologists, you will sometimes get a spectrum of opinions, from "benign" to "benign with malignant potential" to "early malignant change" to outright "cancer." When such a patient gets well without treatment or after unorthodox treatment, as he sometimes does, just what disease did he have?

Cousins cites papers on arthritis, but he makes the error of expanding their conclusions to include collagen diseases in general, and his own case. For instance, Sahud and Cohen describe patients with rheumatoid arthritis with low blood levels of vitamin C (7). They say aspirin is antagonistic to vitamin C, so they advise patients with rheumatoid arthritis to take vitamin C. But Mr. Cousins never had a blood level taken to see whether he had the vitamin C deficiency that the authors he quotes found in their patients. Even if his blood level had been determined and found low, it is not his point. His point is that vitamin C is beneficial even if the blood level is normal. Sahud and Cohen did not advise discontinuing the use of aspirin in rheumatoid arthritis as Mr. Cousins does; they just advised taking vitamin C along with it. In this instance Cousins uses the gambit of reporting only that part of the article of which he approves. Unfortunately for his argument, the authors continue, "Administration of supplemental ascorbic acid to rheumatoid patients receiving a high dosage of aspirin as primary therapy seems warranted,"—not quite a ringing testimonial for vitamin C, especially when we consider the following from the same article, ". . . the use of vitamin C has not been associated with major benefits in the treatment of rheumatoid arthritis." and "There was no relationship between the low platelet levels of ascorbic acid noted in the patients on high aspirin intake and the activity or severity of the rheumatoid arthritis."

Advocating a therapy by associating one observation with another, without proven linkage, is a common fallacy in pseudoscientific logic. Two physicians wrote Mr. Cousins saying they believed the effect of vitamin C on the red blood cell sedimentation rate (and presumably on the disease causing the elevation of the ESR, although it is not reported that they actually said so) was mediated by its ability to disperse red blood cell aggregates. "I interpreted this explanation to mean that ascorbate was useful in restoring the chemical balance in the blood, or what Walter Cannon termed homeostasis." Walter Cannon died in 1945. No one today can know whether that great physician-physiologist would have reacted favorably to this attribution of his theory to the shaky material presented in this book.

Tuberculosis

When Cousins was ten, he spent six months in a tuberculosis sanitarium. He writes: "Patients divided themselves into two groups: those who were confident they would beat back the disease . . . and those who resigned themselves to prolonged and even fatal illness." This tidy choosing up of sides lends itself to a neat conclusion. The boys in his group (the confident ones) had a higher percentage of "discharged as cured" outcomes than those in the other group (the resigned). Luckily for the author's conclusion, there does not seem to have been an in-between group. Apparently every patient had to choose one team or the other.

I am sure it has occurred to Mr. Cousins, although he does not say so, that the group that was gloomier and more lethargic may have had reason to be; its members may have been sicker. The observation is further complicated by the fact that patients with tuberculosis exhibit a certain amount of illogical euphoria, a clinical phenomenon long known to physicians, and an observation that Thomas Mann used as an important motif in *The Magic Mountain,* almost eighty years ago. Unless one accounts for these reservations (and there are several others), I do not see how anyone can draw any conclusions, least of all the author's, that high spirits in patients with tuberculosis are curative. The entire argument is thrown into farce by Mr. Cousins' admission that he was in the sanitarium by error; he did not even have tuberculosis.

Heart Disease

When Norman Cousins was thirty-nine, a routine preinsurance examination revealed a coronary occlusion, of which he had had no knowledge or symptoms. His aunt, who was also the insurance agent, told him that the insurance doctors "said that if I became completely inactive, I might be able to stretch out my life for a year and a half." Here again we learn of physicians whose terrifying predictions and baleful prognosis are relayed through a third party. (I don't know Mr. Cousins' aunt, but I fervently hope that I do not have one who would give me someone else's opinion that I had a year and a half to live if I was lucky.) Mr. Cousins ignored the advice, increased his activity, and believes that this saved his life. It may have. A few days later "[Mount Sinai] hospital cardiograms confirmed the insurance reports." He does not tell us that these physicians who read the reports agreed with the dire prognosis and recommendations for complete inactivity for the months remaining to him. Certainly his physician did not. I think some corroboratory evidence must be offered and judged before this episode can be demonstrated to prove anything.

Longevity

A chapter on Pablo Casals, Albert Schweitzer, and longevity is fascinating and exasperating at the same time. There is scarcely a declarative sentence in this chapter which does not seem arbitrary. For instance, Cousins describes the vigor Casals and Schweitzer exhibited even when in their nineties. He describes the marvelous physical effect playing the piano or cello had on Mr. Casals. Well and good. But he then goes on to say that his morning difficulty in walking, his stooped posture, shuffling gait, and labored breathing were all reversed by effects on his body chemistry mediated by his production of cortisone by a self-induced surge of adrenal gland activity, a surge related to his creative powers. The author does not say that the miraculous transformation *may* have been brought about this way; he says it *was.* Are we to understand that cortisone is the new elixir of life?

Albert Schweitzer is described similarly. These two creative geniuses lived long; therefore, the argument runs, creativity and longevity are linked. Cousins has said, "I believe a connection exists between creativity and longevity, and that people can live many years with illnesses if they have a desire to go on living." This concept, which seems to relate to learning to live with a disease (Mr. Casals is described as having had rheumatoid arthritis, emphysema, and cardiac insufficiency), is subsequently confused with a different idea, that creativity can avert disease. They are not the same thing. In the case of Mr. Schweitzer: "Purpose—another word for creativity—produces the chemical changes that enable the individual to turn back . . . disease attacks." This seems to me a cruel judgment on the characters of all the creative geniuses who died young. They too might have lived to be ninety-five if they had only wanted to, or have reversed crippling infirmities if they had only had the stuff; maybe they weren't as creative as they pretended to be. The fact that two great geniuses lived long does not justify the title of the essay, linking creativity and longevity. The opposite case, "Creativity and Death at an Early Age," would be just as easy to make by selecting different examples. And that very view has been expressed—although, I believe, with no more validity—namely, that many writers and other artists die young, driven by their sacrifice-demanding daimons to self-destruction and martyrdom.

The Cousins thesis may have a distressing effect he certainly does not intend. It may make disabled and dependent sick people feel guilty (the defect is in themselves), and it may provide a rationale to those about them who are only too happy to have an excuse to withdraw their sympathy and support. "I've known a great many people who lived into their 80's and 90's despite [their] diseases," Cousins has said, "but the one thing all these people had in common was that they were creative. They had things they wanted to do; they had no reason to die." Well, I have seen many nonagenarians who did not have Casals' "will to live, faith and good humor" but who, on the contrary, lived on in boredom and bitterness, despair and melancholia. I suggest Cousins visit a home for the aged before he sets his generalizations about longevity in stone.

Emotion and Disease

Cousins' opinions on the relation of motivation and strength of will and the "full exercise of the affirmative emotions" to disease and recovery from disease were taught to me in medical school forty-five years ago. If he discovered these correspondences independently, then he deserves credit, but he does not have priority. The physical effects of suggestion (the faith healer, the shaman, the placebo, the curative shrine) were accepted facts decades ago. Surgeons have known for at least the forty years of my practice never to operate on a patient who says he is sure he is not going to survive the anesthesia. Unexplained does not mean ignored.

On the other hand, it is exhilarating to take care of patients with a will to live. They behave encouragingly differently during sickness. No physician can help but be aware of the variability of the psychologic response of different patients to the same organic disorder, of the fact that the patient's state of mind has a strong influence on his disability. As Cousins says, it is important and valuable to mind and body to instill in a patient an optimistic belief in the certainty of his cure. Yet I do not believe, nor do I know any evidence for the belief, that these measures cure an otherwise irreversible illness. Strong-willed active-minded death-defying patients do die; whether or not they have lived their terminal days well or badly is something else.

There are opinions that support Cousins in this matter and he quotes them. Dr. William Osler said that resistance to disease is related to the patient's faith in the treatment, his optimistic state of mind, and the comfort his attendants grant him. This response can be elicited, Osler said, to resist infectious disease (tuberculosis) and neoplastic disease (cancer). This belief has not had solid scientific substantiation in the more than sixty years since Osler's death. Cousins also quotes Dr. Alexander Leaf, who believes that the will to live mobilizes the body's natural mechanism of resistance to disease, a response effected via the immune system,—which is why, he says, most diseases are self-terminating.

Conclusion

Mr. Cousins had a serious but not life-threatening illness. He has written a book about it. I think it is a very bad book although written by one of the best men I know.

I do not claim that medicine belongs exclusively to physicians, scientists, and technicians. The potentials of biochemical manipulations mandate the involvement of philosophers, social scientists, and representatives of the general public, who must help resolve the ethical problems science poses, resist the dehumanization of medicine, and guide medical practices. Thus I applaud Mr. Cousins' advocacy of a balanced life, a hopeful frame of mind, and his emphasis on the unity of mind, body and world. I am, however, disturbed by his illogical analogies and his elevation of uncorroborated data into therapeutic certainty.

The range of the unknown is vastly larger than that of the known. But no one has the right to fill the void with disparate data arranged in an arbitrary order. The band of adherents to the uses of reason, and to the search for that knowledge that can be discovered only through reason can ill afford deserters of Norman Cousins' caliber.

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Rapid On-line Drug Information System for Intensive Care Units

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Abstract

We have developed a rapid on-line system for retrieving clinically relevant information on drugs. We are using a PDP 11-70 with 96K core and 2K cache memory. Bulk storage is provided by an 88 Mbyte magnetic disc. Input and output is from a 24 line, 80 character per line, video terminal. Information on drugs is stored on discs. Several programs have been written in FORTRAN to manipulate these files. PHARM is a program designed for use in clinical areas of the hospital. This program rapidly retrieves desired information on drugs from the data files. PHARMED is a text editor designed for entering and updating of information in the data files. This system has been installed and is in regular and frequent use in our coronary care unit.

Obtaining information on drugs rapidly in clinical settings is a difficult problem faced every day by clinicians. Research in the library may be time consuming and not yield the appropriate information. Standard sources of information may in some ways be obsolete by the time of publishing, and package inserts may not contain the desired specific item of information. The problems are especially critical in the intensive care unit when a decision may have to be made within minutes.

The computer offers a unique method for clinicians to rapidly acquire information on drugs. Here, the information may also be updated frequently to provide the latest knowledge. For a system to be effective, it should have certain characteristics. It should allow the user to find desired information rapidly and be easy to use with minimal training. Because medical personnel are often resistant to the use of the computer in clinical settings (1, 2), this wariness must be overcome. In fact, the system can serve as an introduction of medical personnel, especially to computer systems. In addition, high quality, accurate and up-to-date information must be presented in an easily readable format.

The digital computer has been used in the past as a teaching aid in medicine utilizing complex and lengthy question and answer programs (3, 5). While this kind of computer application is most useful, because of its complexity it often does not come into routine clinical use. Previously, only preliminary attempts have been made at rapid information retrieval in clinical settings (6, 7). In this paper, we will describe a system that allows even an inexperienced user to retrieve information within one minute. The system is now in routine clinical use in our cardiac care unit by persons, many of whom previously had little experience with computers.

Computer System

This project uses the cardiology computer system which operates in a multi-user environment. The hardware consists of a PDP 11/70 computer with 96K core and 2K cache memory. Bulk storage is provided by an 88 Mbyte magnetic disc and a magnetic tape drive. The operating system is RSX-11M V.3.1. A standard 24 line, 80 character per line video terminal is installed in our coronary care unit. This terminal is hard wired to the central processing unit, and runs at 9600 baud, permitting rapid data transmission. We anticipate installing other terminals at strategic points in the hospital, and hard wiring these terminals to the computer. Users elsewhere in the hospital or in other hospitals will have access to the system by means of an acoustic coupler and use of the telephone lines.

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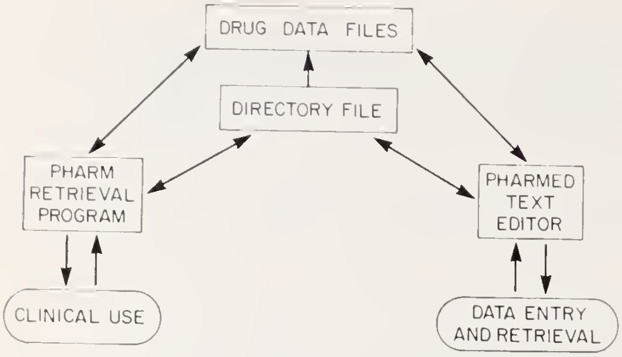


Figure 1

Software

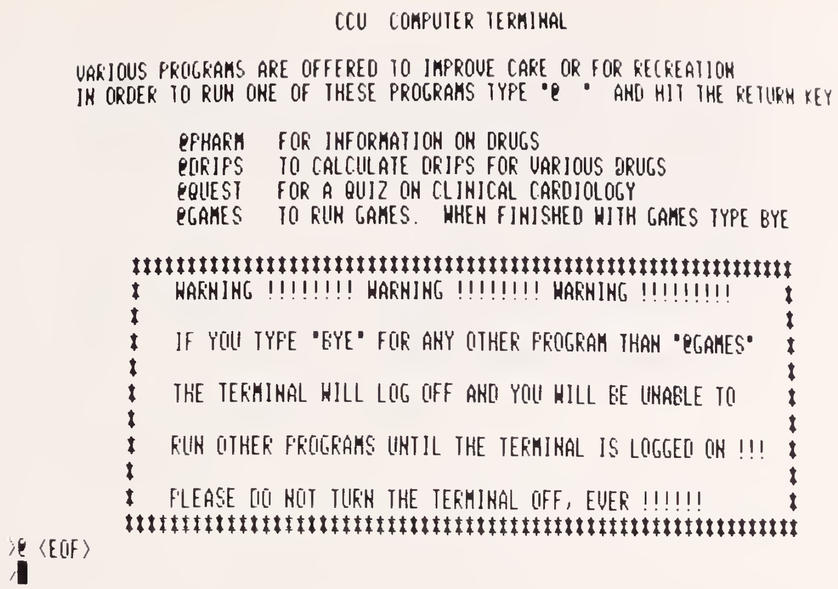
Drug information is stored on disc. Several programs have been written in high level languages (FORTRAN IV) to manipulate the files. PHARMED is a complete text editor used to enter and update information. PHARM is a program to retrieve information in clinical settings. Figure 1 displays the relationship of the data files and the programs that retrieve and edit information.

Information in the drug data files is stored in alphanumeric form with a separate direct access file for each drug. Direct access files offer the advantage over sequential files in permitting rapid access to desired points of information without time of rewinding and in then reading through the file to the desired point. This set-up greatly diminishes disc access time. Each drug file contains 264 lines with 74 bytes (8 bits/byte) per line for a total of 19,536 bytes per file. Therefore, if information on 1000 drugs were stored on the disc, this would be a total of 20 Mbytes, which would not seriously hinder the operation of our computer. The files are divided into 22 line sections. Each section contains information on specific aspects about a drug to be explained below. One section is displayed at a time, filling the screen with information.

There is also a separate directory file on drugs available, with each line in this file containing the generic name of the drug and a code name that is the same as the name of the corresponding drug data file. This code name is an eight character alphanumeric string.

As we have noted, multiple programs have been written in FORTRAN IV to manipulate these files. FORTRAN is not an ideal language for word processing, but it is readily available on most minicomputers, and our entire system could be transferred to another computer with only minor modifications. In order to create or edit the drug data files, a text editor called PHARMED, written in FORTRAN, was developed. This editor is simpler to use than most system text editors. In addition, the RSX-11 text editor allows only creation and editing of sequential data files, so that to do word processing of direct access files, a text editor in FORTRAN was necessary. Using this system, information can be entered into data files by personnel with minimal computer training. This text editor permits creation of new drug files, cataloging of the drugs available in the file, entering of new drugs into the directory file, and editing of information in existing drug files. An elaborate protection code has been devised to prevent inexperienced personnel from destroying data files. All editing is done on temporary files. After information is reviewed, this edited file is renamed with the code name in the drug directory file. Only then does the edited file become available to the user in clinical settings. Temporary files are accessed by entering a preassigned code number. Personnel who wish to edit a temporary data file must enter the assigned code number, thus allowing access only to the temporary file on which they are working. More experienced personnel have different code numbers which allow access to all files in the system.

PHARM is the program used to retrieve information in clinical settings. This program requires no training to use, and allows even an inexperienced user to find desired information in less than one minute. The user in a clinical setting who wishes to find information about any drug in the system types @PHARM, (the symbol "@" runs a command file which in turn runs the PHARM program) and then the program displays on the terminal a choice of drugs. The PHARM program does this by reading the generic names of the drugs in the directory in the directory file and then displaying these names on the terminal. The user then enters the number of the drug he wishes information on. The program then reads from the directory file the code name of the drug of choice. Then general information on the drug is read from the drug data file and displayed on the terminal. This section of general information includes a brief description of the drug, dosage forms available, and cost. The user then has the option of selecting another drug, getting more detailed information on the drug, or getting out of the program. The choices of detailed information are chemistry, physiologic actions, indications and dosage, contraindications, modifications of dosage in disease states, side effects and adverse reactions, pharmacokinetics (two sections), drug



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                        CCU  COMPUTER TERMINAL

VARIOUS PROGRAMS ARE OFFERED TO IMPROVE CARE OR FOR RECREATION
IN ORDER TO RUN ONE OF THESE PROGRAMS TYPE "@  "  AND HIT THE RETURN KEY

           @PHARM   FOR INFORMATION ON DRUGS
           @DRIPS   TO CALCULATE DRIPS FOR VARIOUS DRUGS
           @QUEST   FOR A QUIZ ON CLINICAL CARDIOLOGY
           @GAMES   TO RUN GAMES.  WHEN FINISHED WITH GAMES TYPE BYE

      !!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
      !   WARNING !!!!!!! WARNING !!!!!!! WARNING !!!!!!!!       !
      !                                                          !
      !   IF YOU TYPE "BYE" FOR ANY OTHER PROGRAM THAN "@GAMES"  !
      !                                                          !
      !   THE TERMINAL WILL LOG OFF AND YOU WILL BE UNABLE TO    !
      !                                                          !
      !   RUN OTHER PROGRAMS UNTIL THE TERMINAL IS LOGGED ON !!! !
      !                                                          !
      !   PLEASE DO NOT TURN THE TERMINAL OFF, EVER !!!!!!       !
      !!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
>@ <EOF>
/█
```

interactions, pathophysiologic factors, and references. Each area of information is 22 lines long except for the pharmacokinetics section which is 44 lines long. The user selects the area of detailed information by number, and the appropriate information is displayed on the terminal. If the user selects the section on pharmacokinetics, the first 22 lines are displayed, and then, on cue from the user, the next 22 lines are displayed. After the user has finished reviewing the information, he will be given the option of selecting another area of interest. The user can sequentially access as many areas as he desires, or at any point choose a new drug or get out of the program.

Several other programs designed for clinical use written in FORTRAN can be accessed in the same manner as the PHARM program. This has been instituted to familiarize personnel with the computer by using "user-friendly" terminals.

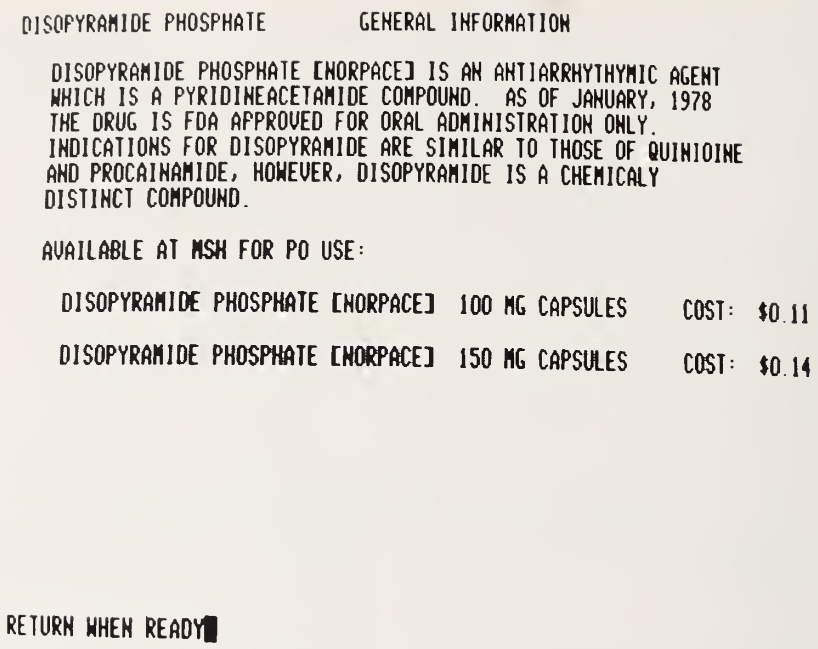
The RSX-11M V3.1 operating system is a multiuser time sharing system. Several users can have access to the system at the same time, including multiple users of the PHARM program. The drug data files are simultaneously accessible to all users. Thus, two users at separate terminals in different parts of the hospital can have access to information on any drug at the same time. The terminal in the cardiac care unit is left logged on at all times to increase the speed and simplicity of the system. Thus, on-line drug information is available 24 hours a day, 365 days a year. A menu of the choices of programs available, including the PHARM program, with instructions is shown whenever a program is not running, and reappears after the program finishes running (Fig. 2). The text editor is not directly available at terminals in clinical areas.

Sources of Information

Information on drugs was gathered from the medical literature. This information was reviewed by members of the divisions of clinical pharmacology and cardiology before being entered into files for clinical use. Information in existing files is reviewed on a monthly basis.

Content of Data Files

An example of the information stored is shown in the following figures in which a portion of the disopyramide (Norpace®) data file is displayed. Figure 3 shows the section of general information photographed directly from the computer screen. This section is always shown first when a drug is selected. There is a brief comment on the drug, then available dosage forms and also cost (which is otherwise rarely presented to clinicians). Figure 4 shows the section on actions on the cardiovascular system. Note the division into sections on "electrophysiology," "hemodynamics," and "electrocardiography (ECG)." The bracketed numbers in the text refer to papers in the reference section. Figure 5 shows the section on side effects and adverse reactions, divided into "common," "infrequent," and "rare" reactions. Note the inclusions of toxic serum levels. Figure 6 shows the first half of the pharmocokinetics section. Information on absorption, distribution, metabolism, excretion, time course of action, protein binding, and blood level is displayed. Figure 7



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DISOPYRAMIDE PHOSPHATE       GENERAL INFORMATION

  DISOPYRAMIDE PHOSPHATE [NORPACE] IS AN ANTIARRHYTHYMIC AGENT
  WHICH IS A PYRIDINEACETAMIDE COMPOUND.  AS OF JANUARY, 1978
  THE DRUG IS FDA APPROVED FOR ORAL ADMINISTRATION ONLY.
  INDICATIONS FOR DISOPYRAMIDE ARE SIMILAR TO THOSE OF QUINIOINE
  AND PROCAINAMIDE, HOWEVER, DISOPYRAMIDE IS A CHEMICALY
  DISTINCT COMPOUND.

  AVAILABLE AT MSH FOR PO USE:

    DISOPYRAMIDE PHOSPHATE [NORPACE]  100 MG CAPSULES     COST:  $0.11

    DISOPYRAMIDE PHOSPHATE [NORPACE]  150 MG CAPSULES     COST:  $0.14




RETURN WHEN READY█
```
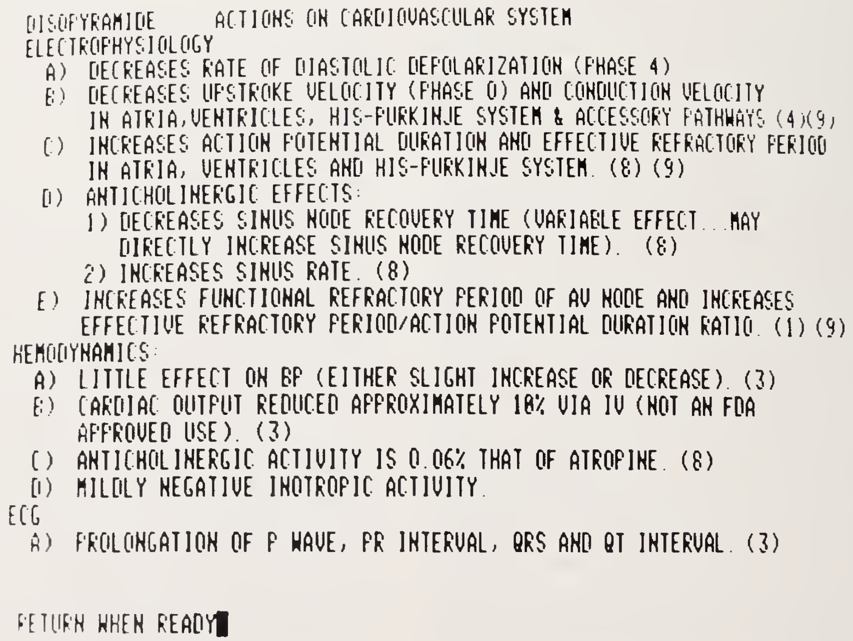

shows the second half of the Pharmacokinetics section. Here, a graph displays blood level of disopyramide during intermittent oral dosage in a typical patient. Curves with and without a loading dose are displayed. Each section fills the screen with information which is displayed in a logical and easily readable format.

Information on drugs is being accumulated by class. First information on cardiovascular drugs has been gathered, reviewed, and entered into the computer. This group includes sympathetic and parasympathetic agonists and antagonists, cardiac glycosides, antiarrhythmics, nitrates, diuretics, and other antihypertensives. This section is largely complete. We are also entering the multiple new antiarrhythmic drugs that are now coming into use. In addition, we are now beginning to enter other frequently used drugs, such as anti-



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DISOPYRAMIDE     ACTIONS ON CARDIOVASCULAR SYSTEM
ELECTROPHYSIOLOGY
  A)  DECREASES RATE OF DIASTOLIC DEPOLARIZATION (PHASE 4)
  B)  DECREASES UPSTROKE VELOCITY (PHASE 0) AND CONDUCTION VELOCITY
      IN ATRIA,VENTRICLES, HIS-PURKINJE SYSTEM & ACCESSORY PATHWAYS (4)(9)
  C)  INCREASES ACTION POTENTIAL DURATION AND EFFECTIVE REFRACTORY PERIOD
      IN ATRIA, VENTRICLES AND HIS-PURKINJE SYSTEM. (8) (9)
  D)  ANTICHOLINERGIC EFFECTS:
      1) DECREASES SINUS NODE RECOVERY TIME (VARIABLE EFFECT...MAY
         DIRECTLY INCREASE SINUS NODE RECOVERY TIME).  (8)
      2) INCREASES SINUS RATE. (8)
  E)  INCREASES FUNCTIONAL REFRACTORY PERIOD OF AV NODE AND INCREASES
      EFFECTIVE REFRACTORY PERIOD/ACTION POTENTIAL DURATION RATIO. (1) (9)
HEMODYNAMICS:
  A)  LITTLE EFFECT ON BP (EITHER SLIGHT INCREASE OR DECREASE). (3)
  B)  CARDIAC OUTPUT REDUCED APPROXIMATELY 10% VIA IV (NOT AN FDA
      APPROVED USE). (3)
  C)  ANTICHOLINERGIC ACTIVITY IS 0.06% THAT OF ATROPINE. (8)
  D)  MILDLY NEGATIVE INOTROPIC ACTIVITY.
ECG
  A)  PROLONGATION OF P WAVE, PR INTERVAL, QRS AND QT INTERVAL. (3)


RETURN WHEN READY█
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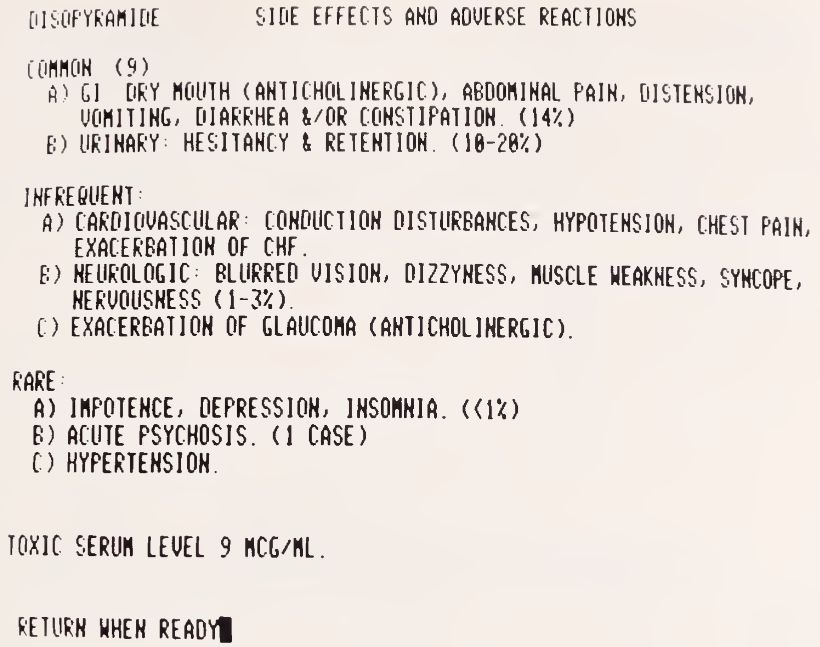

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DISOPYRAMIDE         SIDE EFFECTS AND ADVERSE REACTIONS

COMMON  (9)
  A) GI  DRY MOUTH (ANTICHOLINERGIC), ABDOMINAL PAIN, DISTENSION,
     VOMITING, DIARRHEA &/OR CONSTIPATION. (14%)
  B) URINARY: HESITANCY & RETENTION. (10-20%)

INFREQUENT:
  A) CARDIOVASCULAR: CONDUCTION DISTURBANCES, HYPOTENSION, CHEST PAIN,
     EXACERBATION OF CHF.
  B) NEUROLOGIC: BLURRED VISION, DIZZYNESS, MUSCLE WEAKNESS, SYNCOPE,
     NERVOUSNESS (1-3%).
  C) EXACERBATION OF GLAUCOMA (ANTICHOLINERGIC).

RARE:
  A) IMPOTENCE, DEPRESSION, INSOMNIA. ((1%)
  B) ACUTE PSYCHOSIS. (1 CASE)
  C) HYPERTENSION.


TOXIC SERUM LEVEL 9 MCG/ML.


 RETURN WHEN READY█
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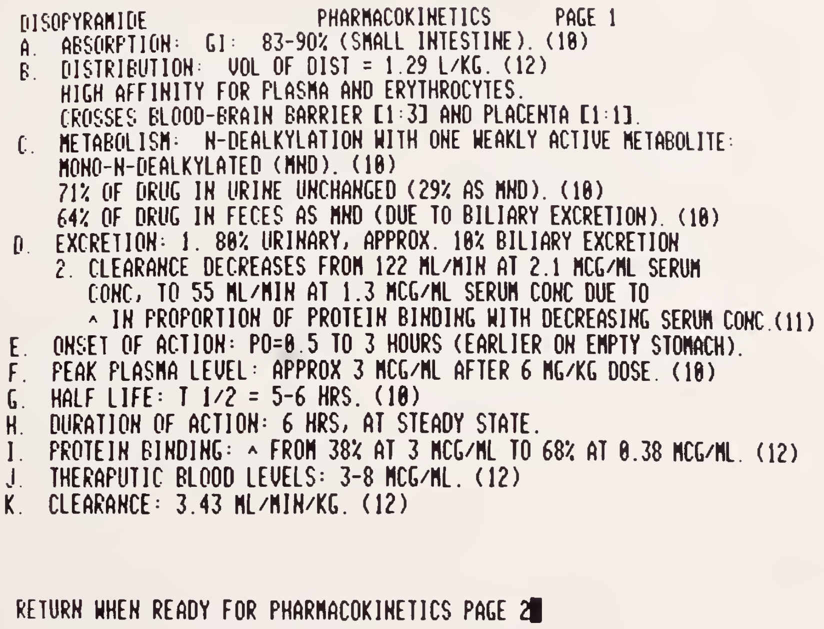
coagulants, antibiotics, and psychotropic drugs into the system.

Use of the System

We are currently evaluating the use of the system and impact on medical care. Whenever a user runs the PHARM program, a separate program called PHATES is run first. This program asks the user several questions about who he or she is, and why he or she is using the system. This information plus the time of day when the program runs are stored in a data file. Some preliminary data is presented in Table I. Thus, we see that multiple categories of medical personnel are actively using the system frequently.

Discussion

Finding clinically relevant information on drugs rapidly is often difficult. No one source pro-



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DISOPYRAMIDE                PHARMACOKINETICS      PAGE 1
A.  ABSORPTION:  GI:  83-90% (SMALL INTESTINE). (10)
B.  DISTRIBUTION:  VOL OF DIST = 1.29 L/KG. (12)
    HIGH AFFINITY FOR PLASMA AND ERYTHROCYTES.
    CROSSES BLOOD-BRAIN BARRIER [1:3] AND PLACENTA [1:1].
C.  METABOLISM:  N-DEALKYLATION WITH ONE WEAKLY ACTIVE METABOLITE:
    MONO-N-DEALKYLATED (MND). (10)
    71% OF DRUG IN URINE UNCHANGED (29% AS MND). (10)
    64% OF DRUG IN FECES AS MND (DUE TO BILIARY EXCRETION). (10)
D.  EXCRETION: 1. 80% URINARY, APPROX. 10% BILIARY EXCRETION
    2. CLEARANCE DECREASES FROM 122 ML/MIN AT 2.1 MCG/ML SERUM
       CONC, TO 55 ML/MIN AT 1.3 MCG/ML SERUM CONC DUE TO
       ^ IN PROPORTION OF PROTEIN BINDING WITH DECREASING SERUM CONC.(11)
E.  ONSET OF ACTION: PO=0.5 TO 3 HOURS (EARLIER ON EMPTY STOMACH).
F.  PEAK PLASMA LEVEL: APPROX 3 MCG/ML AFTER 6 MG/KG DOSE. (10)
G.  HALF LIFE: T 1/2 = 5-6 HRS. (10)
H.  DURATION OF ACTION: 6 HRS, AT STEADY STATE.
I.  PROTEIN BINDING: ^ FROM 38% AT 3 MCG/ML TO 68% AT 0.38 MCG/ML. (12)
J.  THERAPUTIC BLOOD LEVELS: 3-8 MCG/ML. (12)
K.  CLEARANCE: 3.43 ML/MIN/KG. (12)


 RETURN WHEN READY FOR PHARMACOKINETICS PAGE 2█
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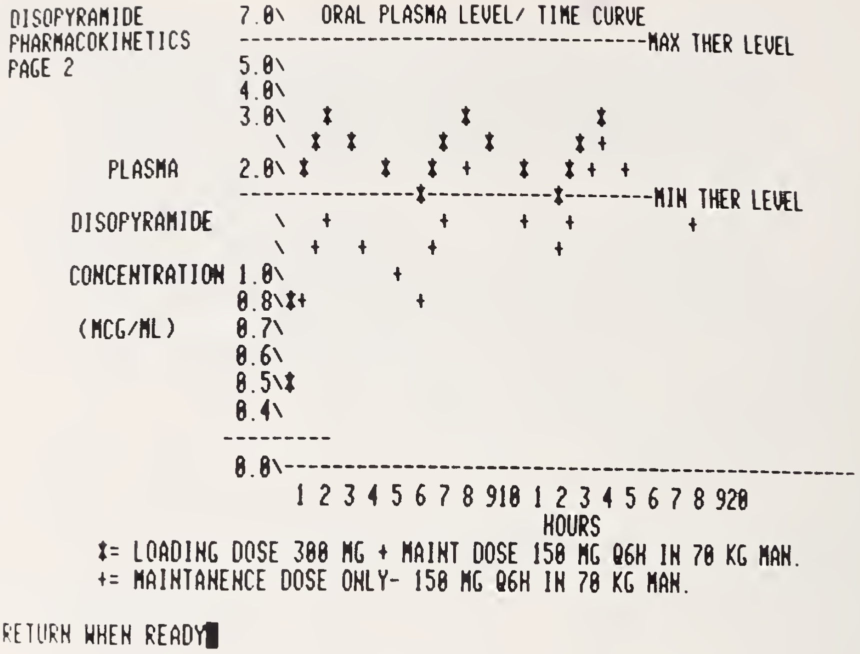

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DISOPYRAMIDE         7.0\   ORAL PLASMA LEVEL/ TIME CURVE
PHARMACOKINETICS     ----------------------------------MAX THER LEVEL
PAGE 2               5.0\
                     4.0\
                     3.0\   ‡           ‡          ‡
                        \  ‡  ‡       ‡   ‡      ‡ +
          PLASMA     2.0\ ‡      ‡   ‡  +    ‡  ‡ +  +
                     ---------------‡-----------‡-------MIN THER LEVEL
       DISOPYRAMIDE     \   +         +      +   +         +
                        \  +   +     +          +
       CONCENTRATION 1.0\         +
                     0.8\‡+         +
        (MCG/ML)     0.7\
                     0.6\
                     0.5\‡
                     0.4\
                    ---------
                     0.0\--------------------------------------------------
                          1 2 3 4 5 6 7 8 910 1 2 3 4 5 6 7 8 920
                                               HOURS
        ‡= LOADING DOSE 300 MG + MAINT DOSE 150 MG Q6H IN 70 KG MAN.
        += MAINTANENCE DOSE ONLY- 150 MG Q6H IN 70 KG MAN.

RETURN WHEN READY█
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vides adequate material. Furthermore, textbooks become out of date before or soon after publication. Information could not always be obtained rapidly in clinical situations before the development of this system. The computer is well suited as a means of storing and retrieving information, because information can be retrieved rapidly, and can be easily entered, updated, and edited. The use of alphanumeric information storage requires more space in bulk storage than coded information, but offers in return the greater detail and subtlety of free text. The major drawback of alphanumeric data storage is that the information is not coded which limits the ability to cross reference data. However, the information stored in this system is easily accessible, extensive, and arranged in an orderly fashion. Specific questions, can be answered very rapidly. In addition, the system can be used as a source of material for programs using coded information storage. For instance, we hope to develop a system in which physicians will be warned on-line whenever a patient is on two drugs which interact. The physician could then have access to the appropriate alphanumeric file for more detailed information on the interaction. Alphanumeric files take up much bulk storage, but as we have pointed out, a moderately large disc can accomodate this system and still have space for many other tasks.

TABLE I

Use of Program PHARM in a Sample Ten-Day Period

Category of User	Number of Times Used
Housestaff	26
Fellow	9
Nurses	33
Medical Student	2
Attending Physician	8
Other	10
Total	88

In the future, we anticipate that this system will be available to other institutions. When the system is operational on the appropriate computer, access could be by way of a terminal with an acoustic coupler and use of the telephone lines.

This system is now in routine clinical use in our cardiac care unit. As pointed out in Table I, the PHARM program was used 88 times in a sample ten-day period of routine clinical use in the CCU. As expected, house staff use the system frequently, but we were gratified to find that nurses have been the most frequent users, accounting for over 38% of the use (Table I).

Thus, we have developed a clinically applicable and relevant computerized method for providing drugs information which should significantly improve patient care. We are presently expanding this system in our facility.

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Extraskeletal Osteosarcoma: Light and Electron Microscopic Study

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Abstract

An elderly woman developed a subcutaneous mass on her back, unattached to any bony structure. Light microscopy showed a typical osteogenic sarcoma infiltrating the adipose tissue and showing a vascular invasion. Histologic differential diagnosis of the extraosseous osteogenic sarcoma is discussed. Ultrastructural study of the tumor revealed calcifying matrix vesicles similar to those found in normal cartilage and bone.

Osteogenic sarcomas very rarely occur as primary tumors of the soft tissues. Because of paucity of the published cases of this unusual entity, an additional instance of extraosseous osteosarcoma, with an ultrastructural study, is hereby reported.

Case Report

An 87-year-old woman was hospitalized for excision of a mass on her back. It had been present for an unspecified period of time, but it was perceived by the patient with certainty about three months earlier. She stated that it enlarged recently, and was associated with discomfort upon movements of the neck and left shoulder. Physical examination showed a roughly round lump measuring about 7 cm in size, tender, partially mobile, well delineated, and not adherent to the skin or fascia. The skin overlying it was normal. The patient had a long standing history of chronic congestive heart failure, arteriosclerosis, hypertension, diabetes, cerebral vascular disease, and severe osteoarthritis, requiring multiple hospitalizations during the past ten years. During one of the admissions for coronary insufficiency, two months previously, a bone scan was done because of severe skeletal pain. The bone scan (with 15 mCi Technetium^{99m} Tc Medronate Sodium (TechneScan® MDP)) revealed a large subcutaneous mass in the left posterior chest wall actively concentrating the radioactive material (Fig. 1). No mention of this mass was found upon review of the patient's multiple prior admission charts. There was no history of previous radiation, trauma or inflammation in this area. There were no other lesions, skeletal or extraskeletal, seen on the scan. Chest x-rays showed no evidence of lung metastases. The mass was excised under local anesthesia. It was hard in consistency, and the central portion appeared necrotic. The tumor involved the fascia, but not the underlying muscle. It appeared to be encapsulated, and it was excised with partly blunt and partly sharp dissection. The patient expired four months later from reasons related to her heart disease. No metastases or recurrence of the tumor were evident clinically. No autopsy was performed.

Pathologic Examination

Gross: The tumor was oval and flat, and measured 6 × 5 × 2.5 cm (Fig. 2). External surface was somewhat nodular, pale gray, and showed small amount of attached fat. The consistency was very firm, and cutting of the tumor produced a gritty sensation. There was a central hemorrhagic necrotic area, which communicated with a pseudocapsule at the periphery. The tumor tissue was nodular, hard and gray. There was a nodular growth at the periphery, relatively well delineated from the adjacent fat. The frozen section consultation was reported as strongly suggestive

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The authors thank Dr. Louis Governale and Dr. Caesar M. Santos for the clinical information on the patient.

Requests for reprints should be sent to: Dr. Marian Waxman, Department of Pathology, Nassau Hospital, 259 First Street, Mineola, N.Y. 11501.

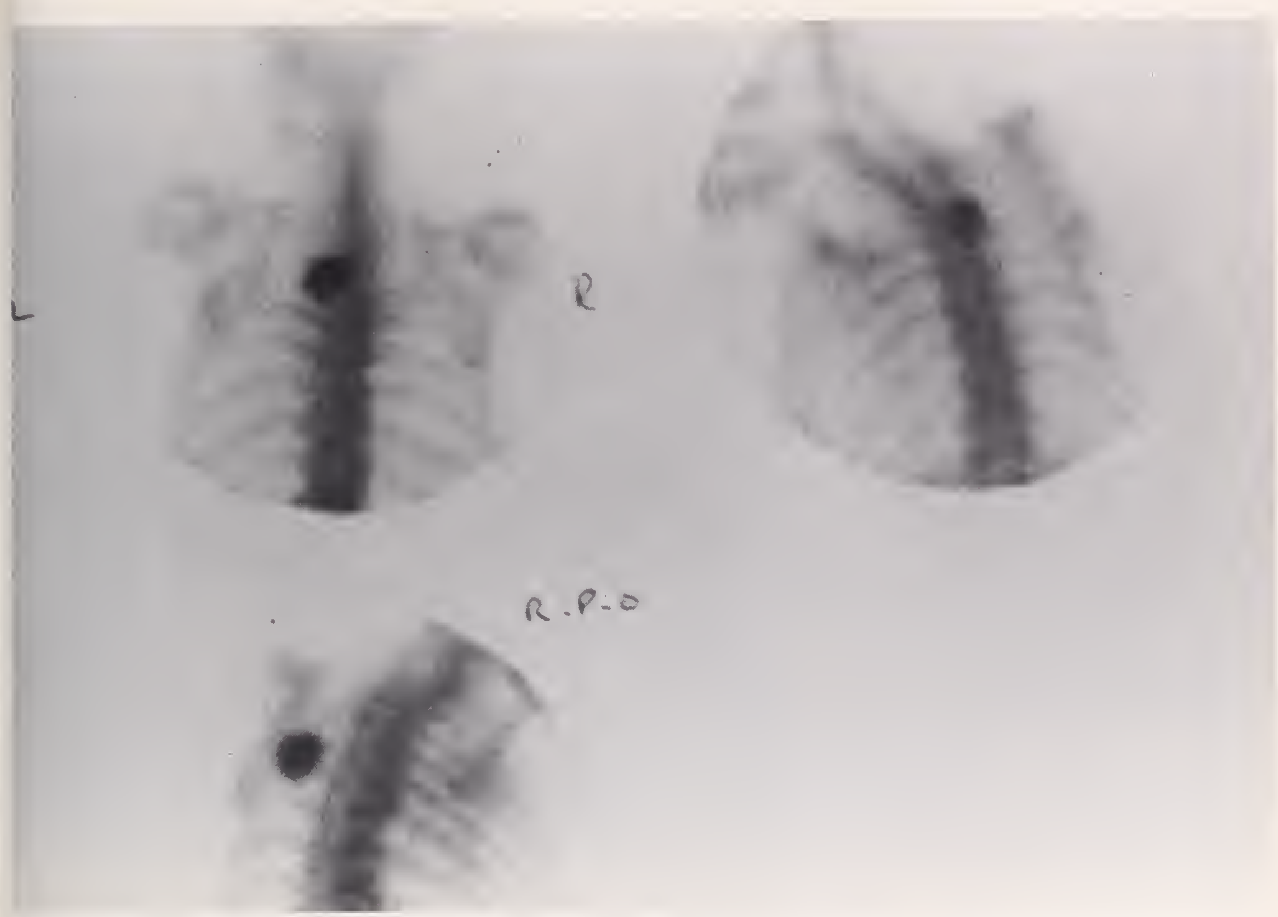

FIG. 1. Bone scan with ^{99m}Technetium Medronate Sodium. An abnormal concentration of the radioactive material is seen in the posterior chest wall.

of extraosseous osteosarcoma, but no further surgery was done because of the patient's poor general health.

Specimen radiography showed a diffuse hazy, rather homogeneous opacity of the tumor (Fig. 3).

Light microscopy: The histologic patterns varied from that of primitive anaplastic sarcoma to a well developed osteogenic sarcoma. Areas of the former were characterized by large undifferentiated and bizarre cells with eosinophilic cytoplasm and irregular vesicular nuclei, and with multiple mitotic figures (Fig. 4). Large areas of the tumor showed widespread malignant osteoid, frequently with calcification and ossification, and often with telangiectatically dilated thin walled blood spaces (Fig. 5), and giant cells of osteoclastic type (Fig. 6). Small focal areas of chondroid were seen. The tumor irregularly invaded adipose tissue at the periphery; a vascular invasion was also identified (Fig. 7). No other sarcomatous elements were found.

Electron microscopy: One mm cubes of fresh tissue from various areas of the tumor were fixed in glutaraldehyde, postfixed in osmium tetroxide, dehydrated in graded alcohols and propylene oxide, and embedded in Epon. Thick sections were stained with toluidine blue. The thin sections were stained with uranyl acetate and lead citrate, and examined with a Phillips 300 electrone microscope.

The predominant tumor cells were irregular in outline and generally elongated (Fig. 8). They displayed slender cytoplasmic projections extending toward the extracellular space, particularly prominent in the areas where osteoid was present. Isolated or in clusters, these cells were connected by occasional intermediate junctions. Rough endoplasmic reticulum was the most prominent cytoplasmic organelle. It was often dilated by a finely granular probably proteinaceous secretion product. Free ribosomes were also fairly abundant, but other organelles were inconspicuous. Nuclei of these cells were somewhat eccentric, large, of irregular outline, and often displayed pseudomultinucleation due to nuclear lobulation. Other tumor cells were also found

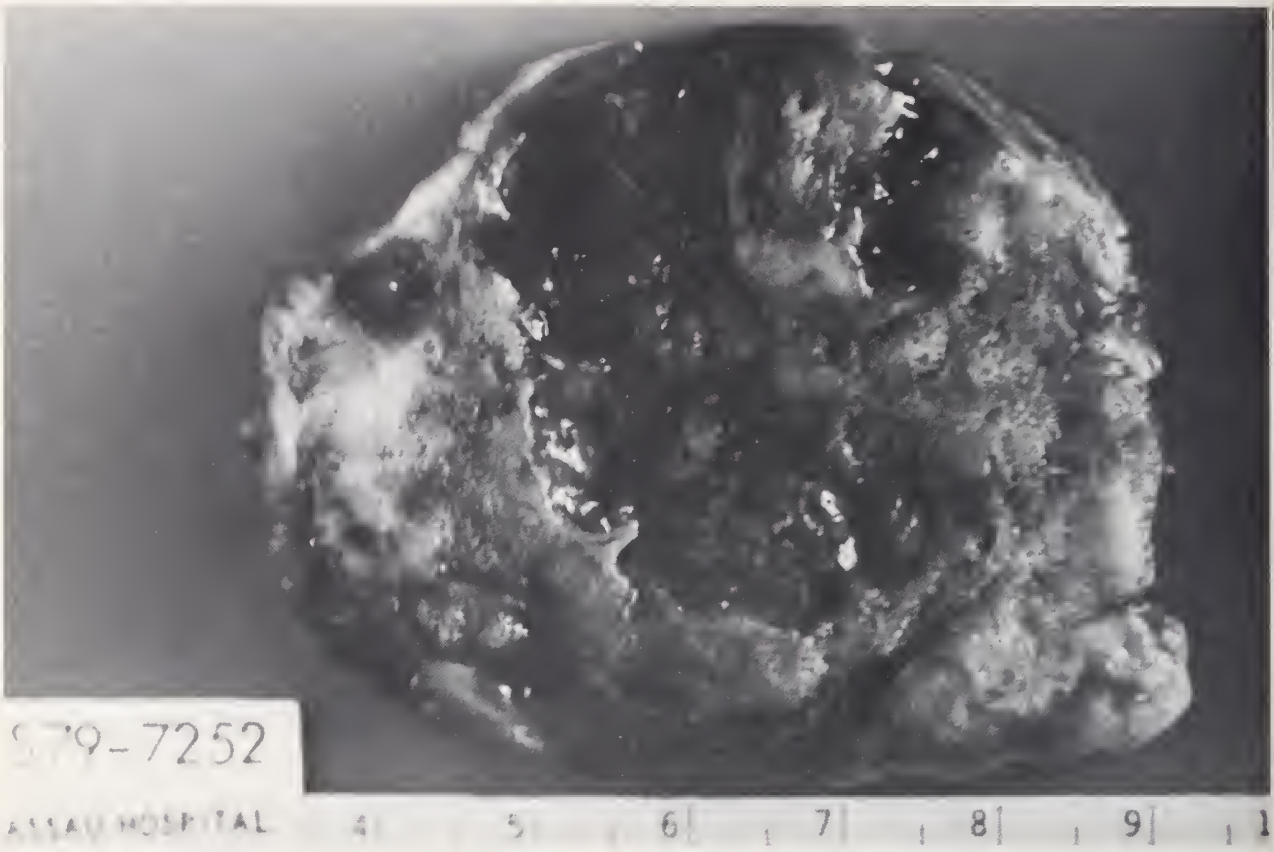
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Fig. 2. Cut section of the tumor showing a gray tissue with central hemorrhage and necrosis.

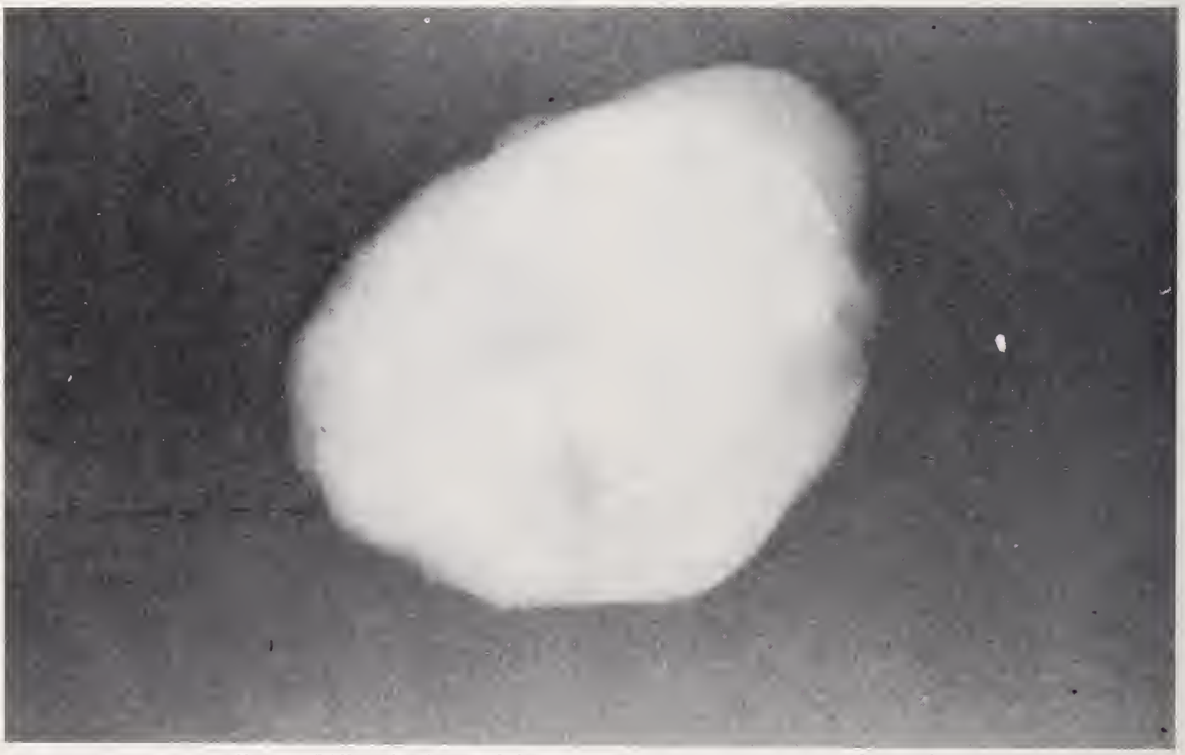

Fig. 3. Diffuse haziness of the tumor seen at the specimen radiography.

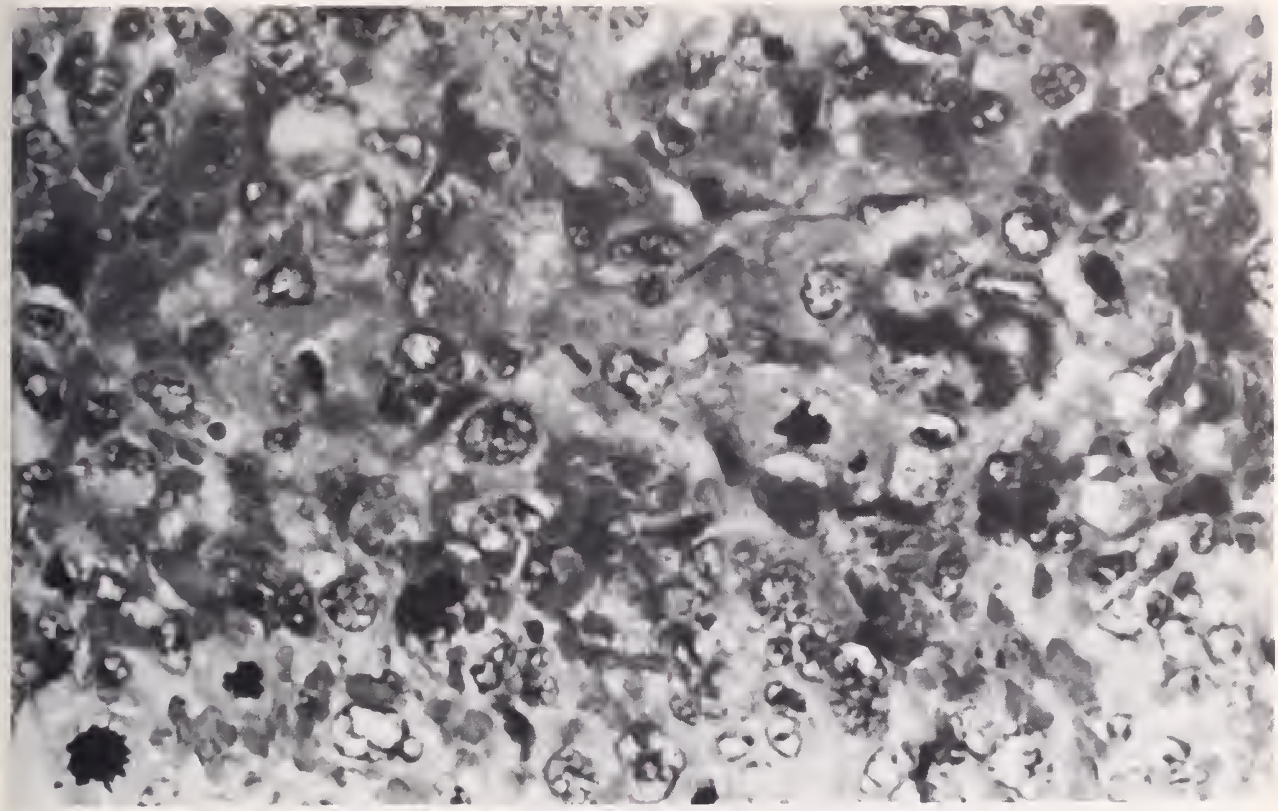

FIG. 4. Undifferentiated mesenchymal sarcoma with multiple mitoses. (H&E, ×250)

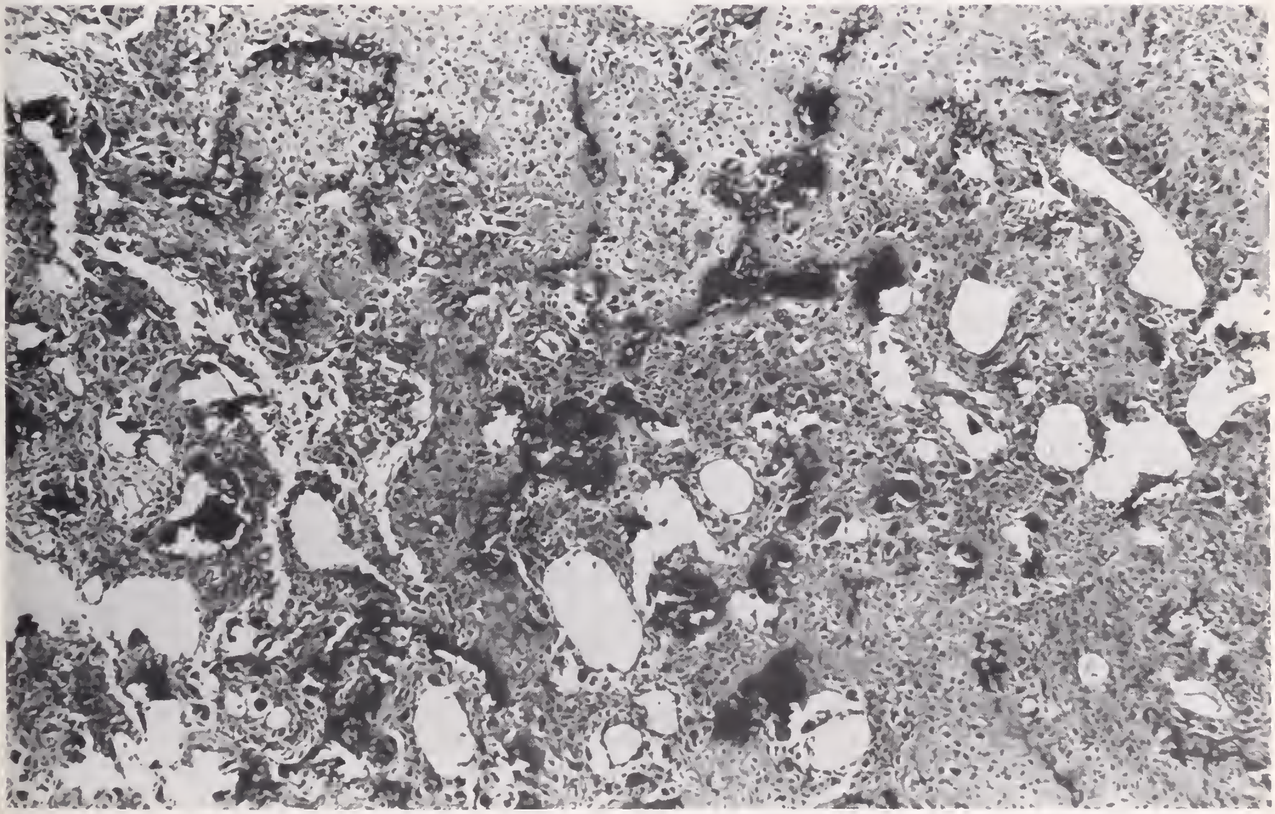

FIG. 5. Malignant osteoid with calcification and ossification, and with prominent dilated blood vessels. (H&E, ×25)

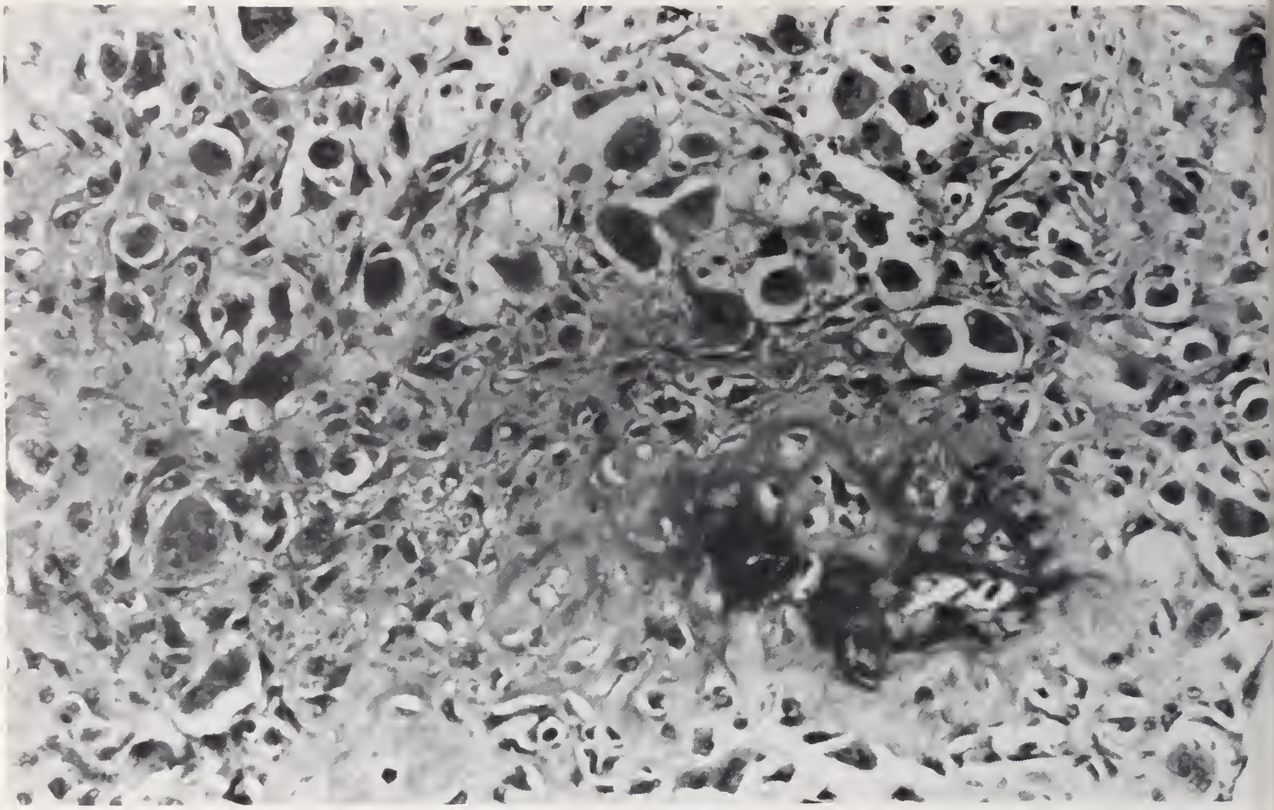

FIG. 6. An area of bone formation surrounded by multiple osteoclastic giant cells. (H&E, ×100)

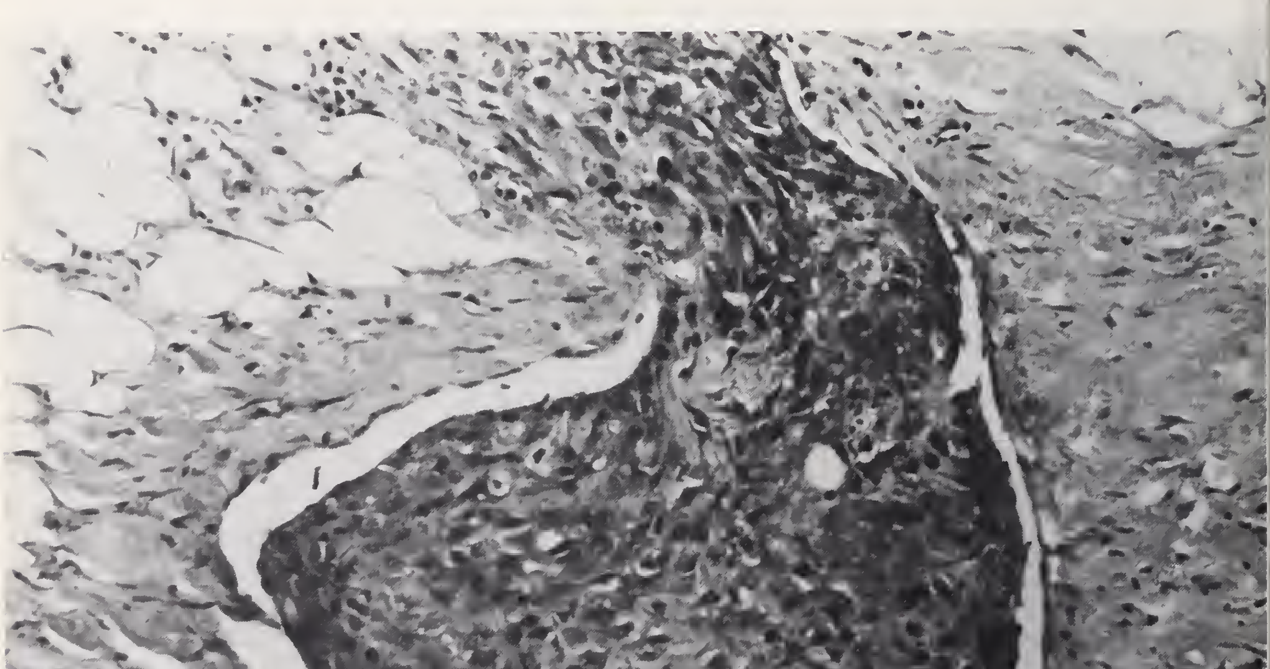

FIG. 7. Vascular invasion by the tumor. (H&E, ×100)

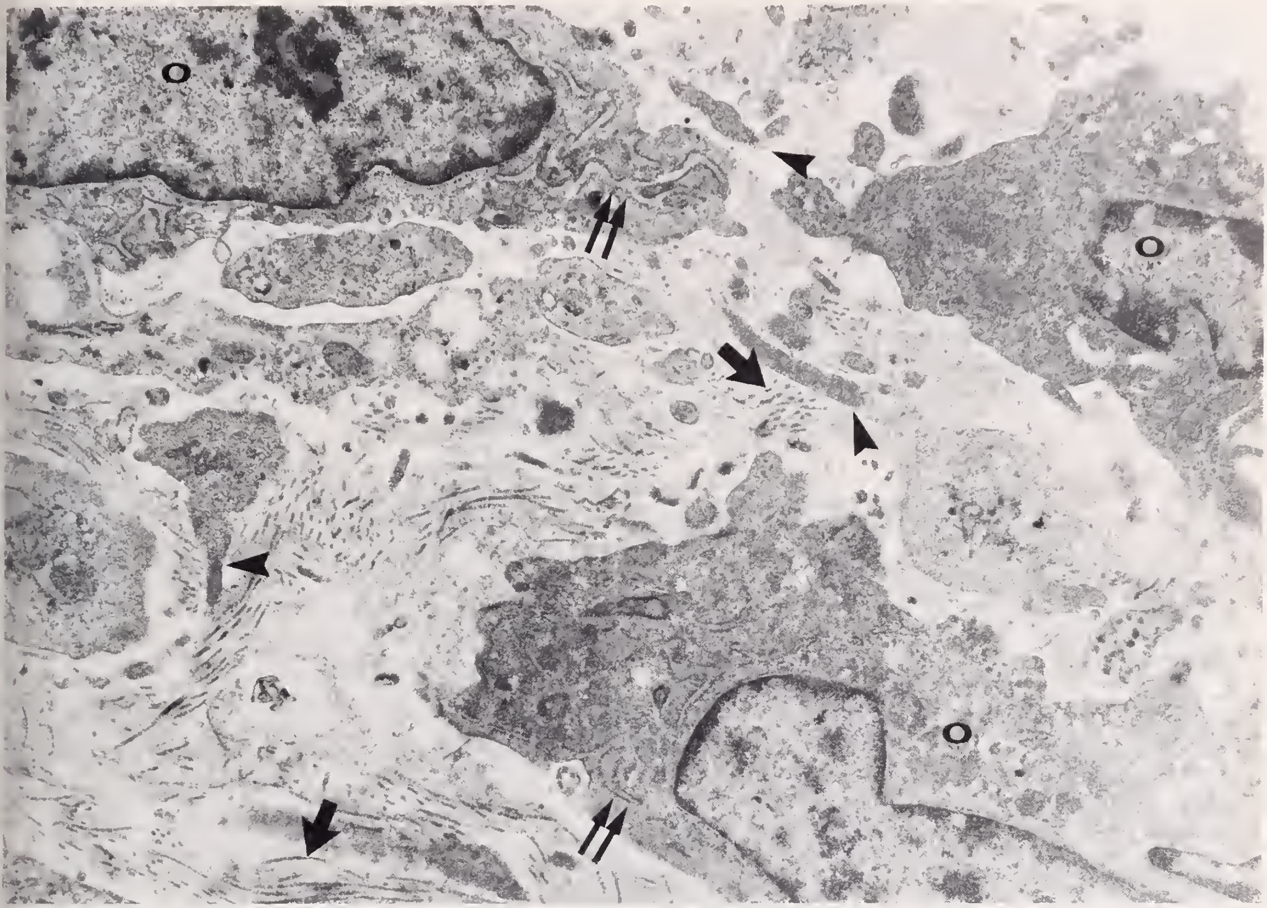

FIG. 8. Osteoblasts (o) with numerous cytoplasmic projections (arrowheads) toward the intercellular space, the latter containing fibrils (arrows). Rough endoplasmic reticulum (double arrows) is seen in the cytoplasm. (orig. magnif. ×11,190)

bearing the characteristics of osteoclasts, namely: multinucleation, abundant mitochondria and short slender surface cytoplasmic projections. Occasional undifferentiated mesenchymal tumor cells were also seen.

The intercellular spaces were occupied mostly by collagen fibrils; generally of normal periodicity and variable width, they were occasionally of the long spacing type. Areas in the immediate vicinity of the cells showed rather scant fibrillary elements; those were generally concentrated at a distance of about one to two microns away from the cell surface, thus creating a lacunar space devoid of the fibers around each cell or cell-cluster. The cytoplasmic projections described previously were particularly prominent in these pericellular lacunar areas (Fig. 9). Beyond them, in the adjacent collagen mesh (osteoid) there were many membrane-bound vesicles measuring 100 to 1000 nm in diameter, containing finely granular material. Some of the vesicles, those far away from the cell surface and within the osteoid, contained hydroxyapatite-type crystals. Elsewhere, more advanced calcifications were apparent, and there, very few, if any, vesicles or fibrils could be discerned.

Discussion

The first large series of osteogenic sarcomas of the soft tissue was that by Fine and Stout (1) in 1956, who reviewed 12 cases accumulated during unspecified period of time, one from their hospital and eleven from the consultation practice. These authors collected additional 34 acceptable case reports from the literature at that time (1). Hajdu (2), in 1979 noted about 125 reported patients with extraosseous osteogenic sarcoma.

Evidently these are exceedingly rare neoplasms. They occur generally in age groups older than those affected by osteosarcoma of the bone, the average being the fifth decade of life. The patient described by us appears to be the oldest one ever reported with this tumor. The males and females are affected about equally (3). The lower extremity and buttock areas are the sites of predilection (2, 4).

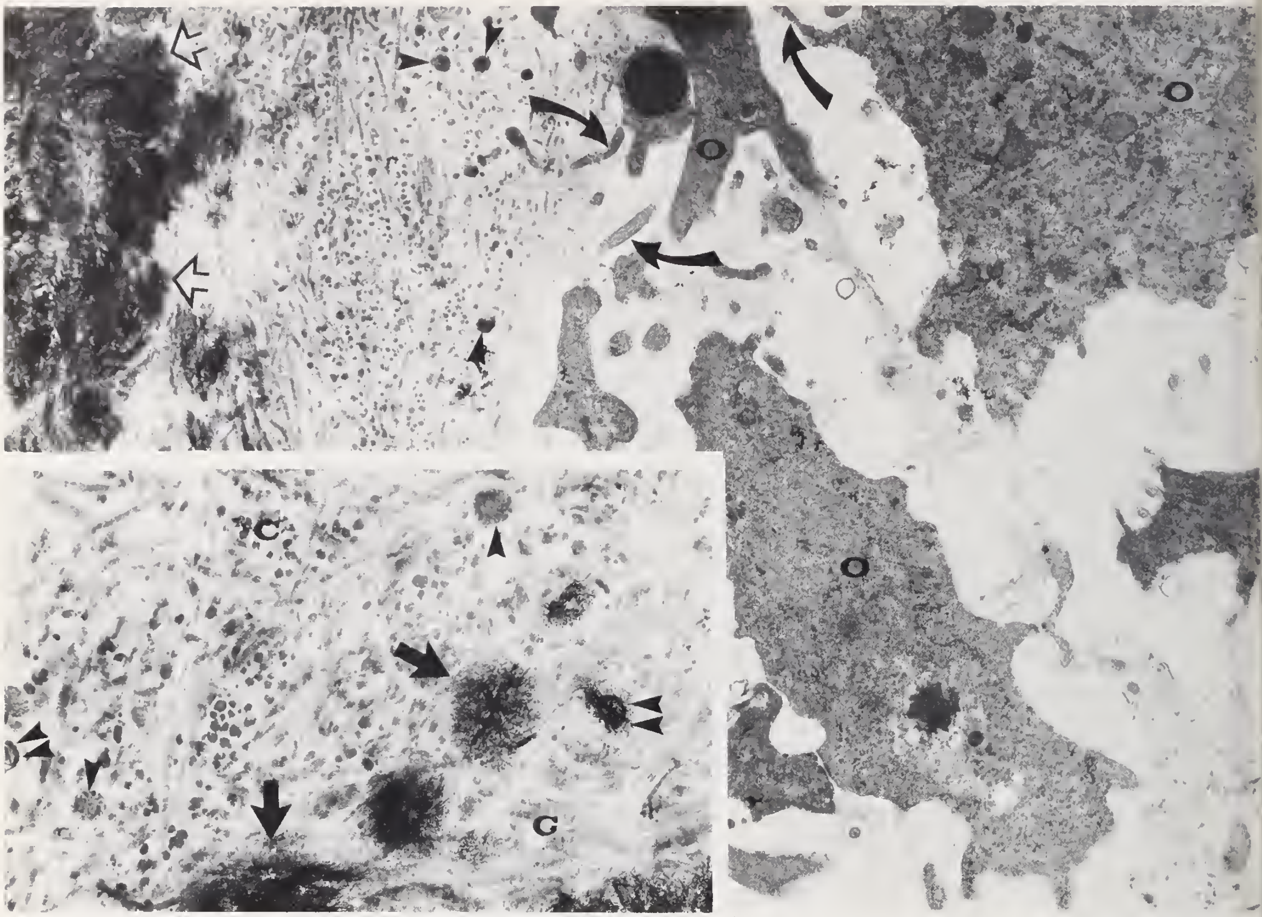

FIG. 9. Osteoblasts (o) with slender cytoplasmic projections (curved arrows); numerous membrane bound vesicles (arrowheads) and calcifying osteoid (open arrows). *Inset:* greater magnification showing the background collagen fibrils (c) of the osteoid an membrane bound vesicles (arrowheads), some undergoing calcification (double arrowheads). Calcification obscuring completel the vesicles (arrows) is also seen. (orig. magnif. ×11,190; inset: ×22,925)

X-rays of the mass can reveal ossification within the tumor, but the precise diagnosis is probably never made clinically. In our case, although the x-rays of tumor failed to demonstrate evidence of calcification, an osteoblastic activity was suggested because of the positive scan. It is likely that the scan activity is related to affinity of the radiopharmaceutical for the immature collagen protein (osteoid) produced by the tumor osteoblasts. Previous local irradiation, inflammation or trauma have all been implicated as possible predisposing factors in individual patients with this cancer (1, 4). Their etiologic importance is, however, in dispute, and in majority of cases, our patient including, these circumstances have not been in evidence. The extraosseous osteogenic sarcomas are characterized by a very malignant clinical course (1, 3–5). Fifty-six patients out of 71 described in three large series, died of their tumor during the follow-up period (1, 3, 4). The lungs are the most frequent site of metastases (1, 3, 4), followed by the lymph nodes (1, 4). The average five-year survival rate computed from five series was 15.6 percent (3). Treatment of these tumors has included the following: an "adequate" local excision, local excision followed by radiation, amputation, either primary or secondary (after a recurrence), or only radiation for inoperable lesion. Chemotherapy has apparently not improved the survival of these patients (3, 4).

Histologically, several entities are to be considered before declaring the tumor an extraskeletal osteogenic sarcoma. Myositis ossificans is characterized by absence of malignant cytologic features, and by central osteoblastic area with peripheral maturation ("zoning"). Calcification and benign bone formation can occur in benign tumors such as pseudosarcomatous fasciitis, or in sarcomas, for example, fibrosarcoma, synovial sarcoma, liposarcoma or malignant fibrous histiocytoma. The extraosseous tumor also has to be differentiated from the parosteal osteosarcoma. Metastatic carcinoma of the breast with metaplastic bone formation is a pertinent differential diagnostic entity, particularly in an elderly woman such as our patient; the diagnosis is based on finding the carcinomatous component which is absent in the osteosarcoma. Finally, if one or more other sarcomatous elements are identified in addition to osteosarcoma, but fibrosarcoma excluding, the tumor should be properly labeled a malignant mixed mesenchymoma (6). The vascular invasion observed in our case is not a frequent finding in extraosseous osteosarcoma. This phenomenon was mentioned by Fine and Stout (1), but it was demonstrated unequivocally in only one out of 34 cases in two other large series (3, 4).

The cell types identified in our ultrastructural study correspond to three of the five cell types described by Reddick and associates (7) in osteosarcomas: osteoblastic, osteoclastic, and mesenchymal stem cells. Myofibroblasts described in some cases of osteosarcoma, mostly of the "fibroblastic" type (7), were not seen in our case. Important in our tumor was the finding of calcifying matrix vesicles, very similar in appearance to those described in normal cartilage and bone (8–10). These have apparently not been described previously in the skeletal (7, 11) and extraskeletal (3, 12) osteosarcomas, with one exception (13). Based on the ultrastructural appearance, it seems to us that these vesicles might arise by detachment or "pinching off" (14) of the most distal parts of the osteoblastic cell processes. Since the smallest, and presumably the earliest, calcific deposits are present within these vesicles, it is likely that the process of calcium deposition begins there; it then extends to the adjacent collagen fibrils, thereby obscuring rapidly all evidence of the preceding initial process. This process of calcification within the extraosseous osteosarcoma appears thus to be very similar to, if not identical with, that occurring normally in a calcifying tissue.

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Intestinal Obstruction: A Neuroanatomic Study

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Several nosologic entities are characterized anatomically in varying degree by hypertrophy, with or without hyperplasia of the mesodermal elements of the bowel wall. These conditions may be congenital in origin (1), caused by inflammation (2), or the result of mechanical obstruction. Whether the resultant changes in the intestinal wall have an underlying unitary mechanism or are due to different processes is critical to an understanding of several important clinical and pathologic entities. There exists a plethora of clinical and pathologic data, but a paucity of unifying concepts, in this area of study of tissue reactions to various stimuli. An experimental study of some of these phenomena may help to resolve this dilemma.

It is well recognized that obstruction of the bowel leads to distention of the hollow viscus proximal to such lesions and to collapse of the distal lumen. Muscular hypertrophy has usually been described in areas proximal to such lesions. The earliest clinicopathologic reference to such an observation occurs in a case report privately published by Miura (3). He reported that: "In intestinal obstruction due to a variety of causes, a massive hypertrophy and hyperplasia of the muscularis propria occurs. If one examines the involved musculature microscopically, one sees the ganglion cells of Auerbach's plexus forming large groups and distributed in broad dense strings or bands. From this microscopic picture, I can suggest that there occurs a genuine hyperplasia and hypertrophy of the neural elements associated with a hypertrophy and hyperplasia of the smooth muscle."

Even in the absence of mechanical obstruction, however, such muscular hypertrophy has been noted in a wide variety of inflammatory conditions (2). Moreover, in cases of congenital aganglionosis of the bowel, muscular hypertrophy has been associated with sprouting and hypertrophy of the neural elements which represent the extrinsic nerve supply to the involved segments. This has occurred in the absence of Auerbach's and Meissner's plexuses which represent the synaptic terminals of these extrinsic fibers (1). Similar changes have been described in various inflammatory diseases of the bowel. (2).

Several experimental studies have been designed to analyze these phenomena, especially in the area of intestinal obstruction. Benninghoff (4) produced obstruction in the small bowel of cats by narrowing the lumen with a ligature. In the few animals that survived, he observed hypertrophy and hyperplasia of the muscular elements and some nerve sprouting in the bowel wall. He was able to achieve positive results in only 2.5% of 40 experiments. Similar findings were obtained in dogs by Okada and Okamoto (5). They were able to produce muscular hypertrophy in the wall if the ileum in six of 33 animals even though they used a 5 mm wide tape as the obstructing mechanism.

Filogamo and Vigliani (6), dissatisfied with the technique of ligature of the bowel, resorted to plication of the small intestine on its antimesenteric border to achieve a suitable narrowing. The area of plication was then covered with an encircling cuff of cellophane. This resulted in an inflammatory reaction and scarring and these, in turn, caused a gradually increasing obstruction. This technique enabled them to avoid vascular and lymphatic obstruction. They report three successful experiments. They note very slight or no changes in the narrowed segment. The proximal, dilated area showed a striking increase in the number and size of nerve cells in Auerbach's plexus when compared with their con-

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trols. The latter consisted of the bowel distal to the obstruction, which they considered normal. These investigators believe the new nerve cells are derived from immature elements previously present. They propose that the neuronal increase and enlargement are correlated with the extension of the territory of innervation. The latter is considered to be the volume of muscle in the wall, which was greatly increased.

In the absence of any data to the contrary, we assumed that ligature of the bowel as done by Benninghoff and by Okada and Okamoto resulted in cutting of the bowel wall as the latter dilated due to obstruction. We decided to obviate this possible difficulty by using a rubber cuff 1.0 to 1.50 cm in length cut from thin walled tubing. The luminal diameter was adjusted by removal of appropriate segments to obtain the desired degree of obstruction.

The studies mentioned above were not designed to demonstrate the temporal and spatial sequence of events involving the different tissue elements of the gut. The present experiments were planned to fill this hiatus and thus possibly lead to a unifying, testable hypothesis to explain the underlying processes involved. The latter interest is broadly concerned with the afferent and efferent impulses which are involved in the central integration and modulation of organ function. These produce the peripheral reactions whose morphologic manifestations represent our experimental end point.

Procedure

Eleven cats, weighing from 1.5 to 2.0 Kg were used in this study. There were nine experimental animals and two laparotomized controls. The animals were immunized against distemper and acclimatized for a week to ten days before surgery. The rubber tubing cuffs were sterilized by preliminary exposure to 10% formalin for two days and then stored in 90% alcohol. At the beginning of the surgical procedure, each was rinsed in sterile saline solution. The surgical procedures were performed aseptically. Under light, intravenous nembutal anesthesia, each animal's abdomen was entered through a midline incision. The jejunum was exteriorized, and a loop in its middle portion was selected for cuffing. The cuff of rubber tubing was inserted between two terminal arcade vessels of the mesentery in a grossly avascular area of the latter. The tubing also enclosed the anastamotic vessels that unite the arcade vessels on the mesenteric side of the bowel. The degree of compression was adjusted by removal of an amount of tubing necessary to give an estimated intestinal lumen of about one millimeter. At this degree of obstruction, the cuff could just barely be moved over the serosa in a proximodistal direction. The cuff was then tied with two silk sutures. After the cuff was secured, the bowel was replaced, covered with omentum, and the abdominal wall repaired in layers.

The animals were observed in single cages for periods ranging from two to seven days. Most animals recovered rapidly from this experimental procedure and took fluids within several hours. Within the next twenty-four hours they were able to eat Purina Cat Chow. By two to three days postoperatively, most of the animals had nonbloody, formed bowel movements. Only two animals vomited, and this ceased two to three days after surgery. These latter animals were given 80 to 100 ml of Ringer's solution subcutaneously daily until they stopped vomiting. The animals were surprisingly playful and tractable.

The animals were sacrificed at preselected times in order to permit the evaluation of the temporal sequence of events. Thus, two animals were sacrificed two days after surgery, two were sacrificed three days postoperatively and the remaining animals were sacrificed on the seventh day after surgery. Under intraperitoneal nembutal anesthesia, an abdominothoracic incision was made exposing the abdominal viscera and heart. Animals were sacrificed by perfusion via the left ventricle with a liter of 10% neutral formalin. The various viscera and the brain and the entire spinal cord were removed. After further fixation in 10% neutral formalin the tissues were cut into blocks. The latter were washed, dehydrated, embedded in paraplast and sectioned serially at 10 micra for the viscera and at 15 micra for the central nervous system. Sections were mounted and stained according to Giemsa's method or with the Bodian silver technique.

Observations

Bowel wall deep to and immediately proximal to the cuff

The serosal surface of the gut was poorly defined due to a deposit of fibrin which was heavily infiltrated with leucocytes and red blood cells. This cuff zone was sharply demarcated from the dilated bowel proximally and the collapsed intestine distally. In the earliest stages, that is, two and three days postoperatively, the fibrinous area contained few fibroblasts; in the seven day specimens significant numbers of fibroblasts were present. In all animals, the lumen was barely visible and the entire bowel wall, though compressed, was heavily infiltrated with leucocytes so that the distinction of the muscle layers was not as clear as usual.

Tissue changes—observed as early as the second day—increased in intensity by the third day and were most marked by the seventh day postoperatively. The neuronal cell bodies in Auerbach's and Meissner's plexuses showed degenerative changes characterized by the disappearance of Nissl substance, cytoplasmic vacuolization, shrinkage of somata and peripheral displacement of nuclei. In some neurons, the nuclei appeared to be extruded from the somata and a residue of faintly stained and poorly localized Nissl substance occupied their former sites. These plexus areas were also compressed and infiltrated with leucocytes. Individual muscle fibers exhibited a decrease in their diameter, cytoplasmic vacuolization and a loss of filaments. Macrophages, containing cellular debris, were scattered throughout the muscle. Both the submucosa and mucosa showed pressure changes. Mucosal necrosis was most marked at the tips of the villi.

The above degenerative changes were accompanied by an increase in the diameter of the nerve bundles coursing between and into the muscle layers, due to an increase in the number of individual nerve fibers comprising the bundles. The compression of the bowel wall made it difficult to evaluate the latter observation. However, mitotic figures were observed in the longitudinal and circular muscle layers, vascular endothelium, fibroblasts and satellite and Schwann cells. The mitotic changes exhibited no regular spatial distribution. All these tissue changes increased in intensity with duration of the obstruction.

Bowel wall proximal to the cuff

As noted previously, in the area immediately proximal to the cuff, the changes were similar to those under the cuff. Tissue changes decreased rapidly with distance from the obstructing lesion.

Despite the dilatation of the intestinal lumen proximal to the obstruction, the intestinal wall was thickened. This change in wall thickness gradually tapered off to a normal diameter depending on the duration and the degree of the obstruction. The circular muscle was the major element contributing to this change in the wall, though the longitudinal muscle was also thickened but to a lesser extent. In both muscle layers, there was an obvious increase in the diameter of the individual muscle fibers (Fig. 1), compared with the control animals and with the bowel distal to the cuff. This (Fig. 2) increase was already present at 48 hours postobstruction and increased in intensity with time. In addition mitotic figures in all stages of the mitotic cycle were seen in both muscle layers but were more numerous in the circular layer. The mitotic figures (Fig. 3) were also observed at 48 hours postoperatively and increased in number with the duration of the experiment, being maximal in the seven day specimens. They were more numerous in the area proximal to than in the area deep to the cuff. Their proximal extent was not determined. In one experiment, gastrointestinal tract obstruction was sufficiently severe as to produce dilatation that extended to the duodenum and stomach. In this specimen, muscular changes, including muscular hypertrophy and hyperplasia with many mitotic figures, were seen in the duodenum.

Similar mitotic changes were seen in the vascular endothelium and media, in fibroblasts,

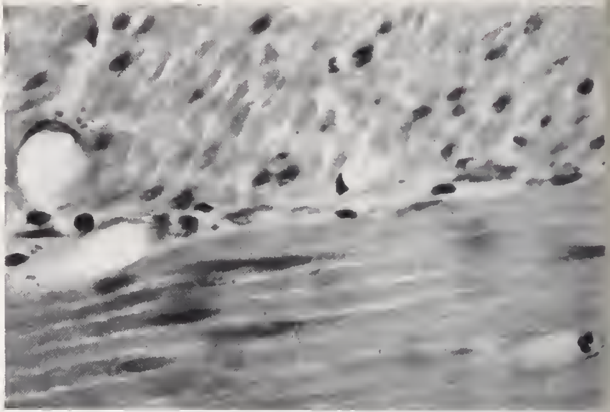

FIG. 1. Photomicrograph of longitudinal and circular muscle layers of jejunum proximal to the obstruction. Surviva time 7 days. Giemsa stain. Mag. ×500

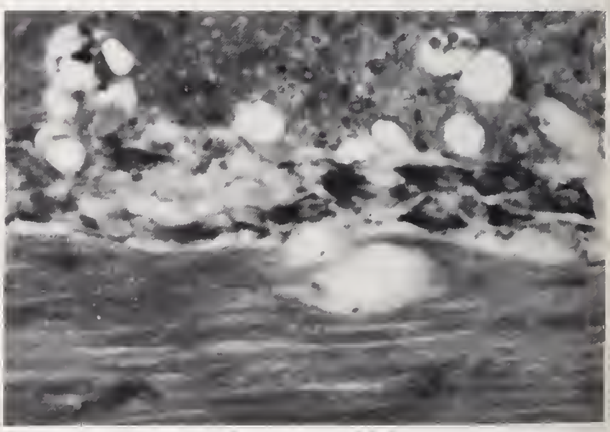

FIG. 2. Photomicrograph of longitudinal and circular muscle layers separated by Auerbach's plexus. Specimen taken distal to obstruction from same animal as Fig. 1.

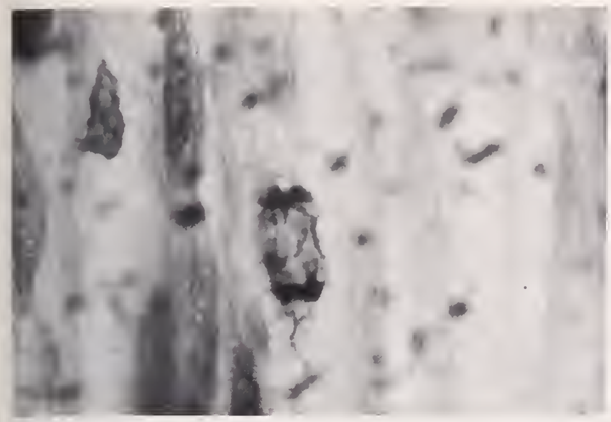

FIG. 3. Photomicrograph of mitotic figure in circular muscle of jejunum. Survival time 2 days. Giemsa stain. Mag. ×1200

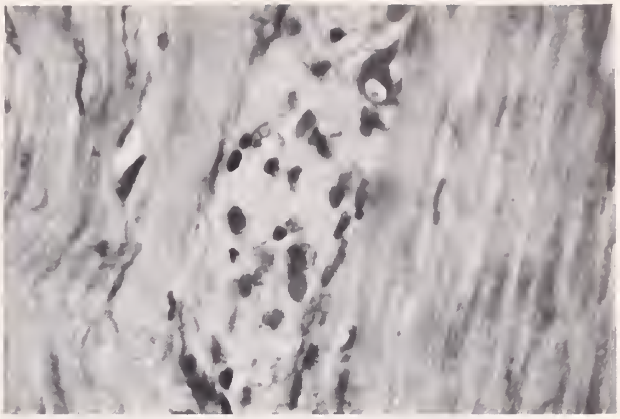

FIG. 5. Photomicrograph of hypertrophied nerve in circular muscle of jejunum. Note the presence of a ganglion cell and numerous Schwann cells. Survival time 7 days. Giemsa stain. Mag. ×500

peritoneal mesothelium and satellite cells in both intramural plexuses as well as in Schwann cells along the nerve fibers in the circular muscle. The increase in satellite and Schwann cells and the hypertrophy of muscle preceded the changes observed in the nerves. The distribution of these findings in the gut wall was random. The circular muscle layer is differentiated into an inner and outer zone (Fig. 4). The significance of this structural difference is not clear; however, the two zones reacted differently to the obstruction. The muscular hypertrophy and hyperplasia involved the outer zone almost exclusively, as evidenced by the numerous mitotic figures observed in the outer zone and the very few mitoses in the inner zone of circular muscle.

As early as the second postoperative day, the muscularis propria showed a slight increase in the diameter of some of its nerve fibers especially in the branches from the myenteric plexus. These altered nerve branches were not uniformly distributed, being most prominent between muscle bundles that form the muscularis propria. In the experiments terminated on the seventh day, however, the nerves formed large trunks which extended out from Auerbach's plexus at oblique angles and reached the submucosa (Fig. 5). These nerve trunks gave off large branches from which multifibered sprays extended between individual muscle fibers, replacing the fine, individual nerve fibers usually observed in this area. Even when individual nerve fibers were present, they often appeared thickened and vacuolated (Fig. 6). The larger trunks as well as their branches were accompanied by numerous Schwann cells and showed varying degrees of leucocytic infiltration.

The bowel distal to the cuff was collapsed and empty of contents. The wall was of normal thickness and demonstrated no structural changes

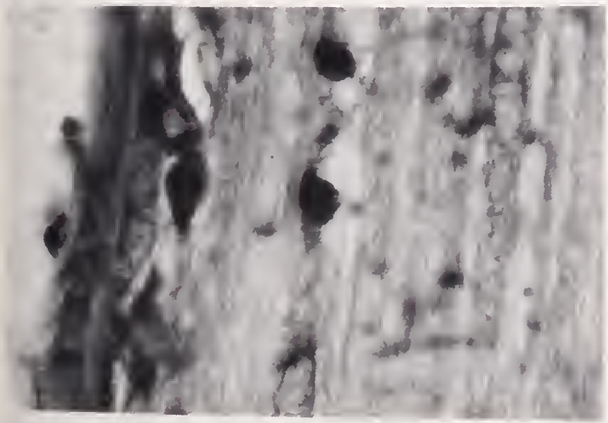

FIG. 4. Photomicrograph showing the presence of the inner dense layer of circular muscle. In the outer layer there is a mitotic figure. Survival time 7 days. Giemsa stain. Mag. ×1200

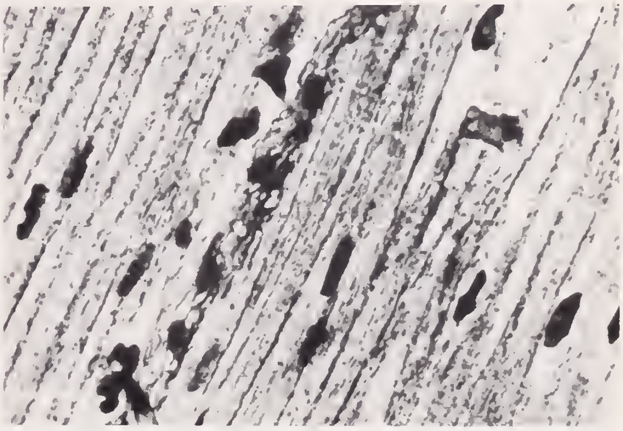

FIG. 6. Photomicrograph of hypertrophied nerve and Schwann cells in the circular muscle of the jejunum. Survival time 7 days. Bodian stain. Mag. ×500

which would serve to differentiate it from the controls.

Discussion

Any analysis of the cellular, spatial, and temporal events produced by our experimental procedure must be based on such anatomic and functional data as are presently available in the area of structure and function of smooth muscle. Such an analysis would take into account not only the unique properties of the smooth muscle cell as an autonomous, "private" entity but also its function in the context of the morphologic complex of which it forms a part. The latter would be its interaction with the other elements of the organism and would be its "public" function in analogy with the concept of vasa privata and vasa publica suggested by Havlicek (7). The harmonious coordination of these two facets of smooth muscle function in the internal milieu of the organism would then, as in the case of the circulation, be dependent on neural and/or hormonal mechanisms.

It is generally accepted that the sliding filament model of muscular contraction is applicable to smooth muscle as well as striated (8). In contrast to striated muscle, which acts through coordination of individual, contractile cellular units, each with its neural synaptic control, the functional unit of smooth muscle in the gastrointestinal tract is the bundle. The bundle is a group of smooth muscle cells acting as a unit. The longitudinal and circular muscle layers are composed of such bundles of almost parallel, interwoven fibers. The bundles are more readily seen in the circular layer, which is the thicker of the two. At irregular intervals, elements of the longitudinal layer project into the circular bundles (9). The circular muscle layer is differentiated into a narrower, dense, central component and a broader, external zone. The external circular fibers are structurally and functionally united by gap junctions; these are absent in the longitudinal fibers and in the central, dense zone. The latter consists of smaller cells which are more closely spaced, so that more nuclei are seen per unit area. The nuclei in this zone are smaller, stain more deeply and have a smooth profile in contrast to the wrinkled outline of the nuclei of the paler cells in the external part of the circular muscle. The dense zone may be two to five cells deep and usually is easily delineated, due to its deeper staining property. The two circular zones are often seen separated by branches of the intrinsic nerve plexus (the plexus muscularis profundus) which connects with Meissner's plexus via large nerve branches passing through the dense muscle layer These innermost, dense layers of the circular muscle have been described at the electron microscopic level in the dog (10) and guinea pig (11) and we have seen them, albeit at the light microscopic level, in the cat.

The nerve terminal in striated, fast muscle is a discrete, sharply demarcated structure consisting of an unmyelinated twig branching out from a terminal node of Ranvier and running parallel to the long axis of the muscle fiber before terminating in it. In contrast, the terminal of a visceral axon in smooth muscle is quite ambiguous. The terminal ramifications are longer than the muscle cells being innervated. Furthermore, there is multiple innervation in which each muscle cell is supplied by several nerve fibers and each nerve fiber innervates several muscle cells. Instead of a sharply localized synaptic area as seen in striated muscle, the autonomic axon in the gut presents numerous varicosities, increasing in number at the terminal end of the fiber. This varicose terminal is in topographic relation to a bundle of smooth muscle cells and not to a single muscle fiber.

Our area of interest, the small intestine, shows an area of innervation typical of the smooth axon variety. In this type of innervation, the nerve fibers spiral within the axon bundles and the Schwann cell covering is interrrupted at intervals as the fibers run parallel to and between the muscle cells. Thus, muscle cells immediately adjacent to a small axon bundle, come into proximity with different nerves within the bundle at different points. The closest approach of a bare varicosity to a muscle cell is about 100 to 200 nm. (12).

The neural elements described above are formed by components of both the extrinsic and intrinsic control systems of the gut. The motor vagal supply of the small intestine probably consists of only several thousand fibers and these must supply hundreds of thousands of intrinsic cholinergic neurons. These, in turn, innervate millions of smooth muscle cells, with relatively wide spaces between nerve and muscle. In general, this results in a diffusion of neural control. More discrete control may occur in pace setting areas of the intestinal muscle. The sympathetic nerve supply from the prevertebral and paravertebral ganglia is considered to provide an even smaller and less discrete innervation to the muscularis propria than the parasympathetic supply.

When experimentally isolated, only cells of the longitudinal layer of the small intestine are able to exhibit spontaneous, apparently myogenic, membrane potential oscillations, termed pace setter potentials (control electrical activity). Such potentials do not occur with isolated circular muscle preparations, which do, however, oscillate when associated with longitudinal fibers. The mechanism involved in the latter phenomenon is not known for certain, but attention is drawn to the observation noted above, the interdigitation of longitudinal fibers into the circular muscle layer. The pace setter potentials, though myogenic, are not invariably associated with contraction of gut muscle. Contraction occurs in a temporal association with action potential spikes (response electrical activity). We are thus dealing with a muscle system in which a spontaneous rhythmic potential pattern is subjected to a variety of extrinsic and intrinsic influences which lead to active potential spikes and muscular contraction. In the context of our experimental design, the observations of Furukawa et al (13) and Ogura et al (14) are of importance. These investigators showed that acetylcholine is released in bowel muscle wall by the stretching of smooth muscle and by a rise of intraluminal pressure. Exposure to increased concentration of the parasympathetic agonist is one mechanism capable of superimposing action potential spikes on the basic control electrical activity leading to response electrical activity and localized muscular contraction. This sequence of events underlies the morphologic phenomena that we have used as the end point in evaluating our experiments.

The rhythmicity of the small bowel is based on the autonomous, spontaneous, slow wave depolarizations of the pace setting areas that periodically increase the excitability or probability of a spike discharge in both muscle layers. We view this autonomous local action as the "private" phase of smooth muscle function. Smooth muscle function then attains a generalized "public" phase under the coordination of intrinsic and extrinsic neural and/or hormonal influences. Since the excitability is also affected by these neural or hormonal influences the resulting contraction is controlled by the interplay of all three elements mentioned. However, the intrinsic, autonomous, "private" component sets the basic pattern for the mechanical events (15).

The apparently spontaneous, though rare, occurrence of mitoses in visceral, and especially in vascular, smooth muscle is well known. Studies have also shown that an increase in work demand on such muscle leads to hypertrophy and even hyperplasia in the involved tissues. In our analysis of the temporal sequences involved, it has become clear that such reactions occur rapidly, that is, within 48 to 72 hours after induction of obstruction. Furthermore, they seem to occur simultaneously in the obstructed segment under the cuff as well as in the dilated proximal segment for a variable distance. It has been shown that in the isolated guinea pig ileum the contraction of the bowel wall on increasing intraluminal pressure could be prevented by enclosing the loop in a glass or perspex tube which prevented or minimized distention (16). This would imply that the hypertrophy and hyperplasia noted in the cuff area in our experiments may be caused by another mechanism or one acting as a supplement to those already discussed. Innes and Nickerson (17) indicate that visceral smooth muscles are generally associated with slow waves of partial depolarization with superimposed action potentials that travel for some distance along adjacent cells. The hypothetical extension of these slow waves of partial depolarization through gap junctions, known to be present in this area, would explain the changes seen deep to the cuff in our studies. The initial changes appear simultaneously in smooth muscle, fibroblasts, endothelial and mesothelial cells. These changes precede any evidence of alteration in the local nerve supply.

The striking increase in the number and size of the nerve fibers appears close to or after 72 hours and is associated with and preceded by an increase in the number of Schwann cells as well as in the frequency of mitoses in these cells. We interpret these changes in the density of nerve supply as a sprouting response to an increase in the area of peripheral field of innervation induced by the experimentally produced hypertrophy and hyperplasia. This would be analogous to the response induced by partial denervation of striated muscle in which the remaining nerves sprout side branches that grow into the adjacent muscle deprived of nerves (18). Another point of interest relating to the adaptive hypertrophy and hyperplasia with which we are dealing lies in the observation that the ingrowth of nerves in this experimental situation leads to a marked increase in mitotic activity in the involved tissues and that regeneration is not completed in the absence of such an ingrowth (19).

A somewhat analogous problem involving hypertrophy and hyperplasia of tissue elements occurs in the study of tissue regeneration. In this area of investigation, a prominent concept has been the functional demand theory of growth regulation (20). Most of these studies involve the reaction to removal of one or more symmetrical organs or parts of organs or to stimulation of an organ function pharmacologically or via neural excitation. The resulting hypertrophy and hyperplasia indicate that functional overload might be the primary stimulus to such a reaction.

One set of experiments has indicated, however, that overload per se is not sufficient to cause such results. Alho (21) found that the increased salivation caused by pilocarpine does not result in glandular hypertrophy. On the other hand, Wells and Munson (22) and Wells et al (23) showed that repeated amputation of the lower incisors in rats results in hypertrophy of the ipsilateral submandibular gland. This hypertrophy is mediated by the same adrenergic nerves that regulate glandular function. Clearly, excessive secretion of saliva does not cause hypertrophy and hyperplasia of the salivary glands; rather it is the stimulation of the sympathetic innervation which promotes their growth. Thus, it seems that functional activity itself is not the cause of compensatory growth but that activity and growth may both be the effect of a common stimulus, that is, the physiologic demand for function. In the case of smooth muscle it would, therefore, not be the actual muscle contraction but the physiologic need or demand for such increased propulsive force that would lead to hypertrophy and hyperplasia.

In other studies of tissue regeneration, mainly involving striated muscle, it has become clear that optimal reconstruction of the injured tissues occured only in the presence of an adequate nerve supply (24). The latter effect was demonstrable even when nerves not usually present were diverted to supply a tissue. These nerve ingrowths were associated with a striking burst in mitotic activity, usually manifested on the third or fourth day of such experiments reaching its peak on the seventh day.

Cameron (25) feels that compensatory hypertrophy as seen in response to a decrease of tissue mass and adaptive hypertrophy resulting from increased demand are separate reactions. In the latter, the tissue first attempts to meet its increased requirements by increased performance. If equilibrium is not established, structural adaptation takes place with hypertrophy and hyperplasia. In his experience, the morphologic reactions of these two types of tissue change are so close that at times it is very difficult to distinguish between them.

The neural response to visceral distention is not limited to the local intestinal phenomena with which we have thus far dealt. Bilateral cortical activity has been observed by electrical methods, maximal nearest the ansate sulcus, on distention of the gut in the cat. These responses were not affected by section of the vagus. They are considered to be the result of impulses ascending in the spinal cord to reach their destination in a localized area of the cerebral cortex. The detailed pathways and the tracts involved have not yet been determined (26).

Summary

Experimentally induced mechanical obstruction of the jejunum in the cat produced similar structural changes in the intestinal wall deep to and proximal to an obstructive cuff. These included:

1. Degenerative changes in the smooth muscle in the entire longitudinal and outer zone of the circular muscle layers. Individual muscle fibers showed cytoplasmic vacuolization, loss of filaments and decreased diameter. Compression and heavy infiltration of leucocytes obscured the distinction of the muscle layers.
2. Degenerative changes in ganglionic cell bodies, in both Auerbach's and Meissner's plexuses were manifested by disappearance of Nissl substance, cytoplasmic vacuolization, eccentric nuclei and cell shrinkage. These plexus areas were compressed and showed leucocytic infiltration.
3. Increased diameter of nerve bundles coursing between and into muscle layers due to an increase in the number of individual nerve fibers comprising the bundles.
4. Mitotic figures in the portions of the smooth muscle layers which exhibited degenerative changes as well as in vascular endothelium, fibroblasts, satellite cells and Schwann cells. All of these changes increased in intensity with the duration of the obstruction and decreased rapidly with distance from the obstruction.

Structural changes in the dilated, thickened intestinal wall proximal to the obstruction and in the area immediately adjoining it proximally included:

1. Hypertrophy and hyperplasia of the smooth muscle of the entire longitudinal layer and the outer zone of the circular muscle layer. The latter zone contributed more to the thickened wall than the former layer. The increase in the number and diameter of individual muscle fibers was accompanied by mitotic figures in all stages of the mitot-

ic cycle. The mitotic figures were more numerous here than in the wall deep to the cuff.

2. Hypertrophy of some nerve fibers especially in branches which coursed from Auerbach's plexus and were distributed between muscle bundles forming the muscularis propria. The size of the nerve trunks, their branches and individual fibers increased with time. The larger trunks and branches were accompanied by numerous Schwann cells and showed varying degrees of leucocytic infiltration.

Distal to the cuff, the bowel was collapsed and empty. The wall was of normal thickness and showed no structural changes.

The experimental data analysed from the standpoint of smooth muscle activity in the gut leads us to envision the following sequence of events:

1. Increase in functional demand upon locally controlled muscle units leads to increased regional formation of acetylcholine, its agonist.
2. Afferent impulses from this area ascend through the spinal cord to the cortex with branching to various centers in their course.
3. This complex of local and central events leads to the hypertrophy and hyperplasia of the muscle and nerve elements in the gut as well as their ancillary structures.
4. The temporal, spatial and structural limits of this reaction are heuristically considered as a homeostatic reaction in which the local phenomena are under neural and/or hormonal control derived from the central nervous system. This hypothesis will be tested further.

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The Shortfall in Hispanic Health Manpower: The National and Mount Sinai-East Harlem Picture

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> The Mount Sinai Medical Center Mission Statement—Article V: Concern for the Community: "Mount Sinai will be ever sensitive to the social and health care needs of the many different communities it serves. The Center will be a participant in efforts to define and solve health problems in population groups and communities through its capability in developing scientific knowledge, education and service (1)."

Mount Sinai Medical Center serves many community groups and therefore has many opportunities to provide sensitive and responsive health services to diverse New York City populations. Of particular concern are the community of health service users in East Harlem with its large proportion of Puerto Rican Americans.

The cross-cultural and bilingual problem facing providers of health care in East Harlem is part of a growing national health care delivery problem (2). Not only has there been a recent upsurge in immigration from Asian countries but Cubans and other Latin immigrants have been settling throughout the nation. Hispanic Americans constitute a rapidly expanding component of the United States population. According to the 1970 census there were 9.6 million persons of Hispanic ethnicity. Projections have been widely divergent, but by the year 2000, Hispanic Americans are expected to number 55 million or more, the largest ethnic minority in the entire nation. Puerto Rican-Americans who live primarily around New York City number one million according to the 1975 census estimate. Currently, Puerto Ricans represent 16 percent of the total Hispanic population in the United States (2).

The stimuli which lead to migration to the U.S. vary widely. As a result, the U.S. Hispanic population is far from homogeneous socioeconomically. Political exiles, the majority of the Cuban migration, for example, tend to be drawn from a higher socioeconomic and cultural level than agrarian workers migrating to the U.S. in search of employment. The goals and aspirations of an exile group which views migration as a one-way street are quite different from those of a migratory group that shuttles from the island to the mainland on a seasonal basis. Unless Hispanics view their new home as a permanent one, true assimilation is often impossible.

What characterizes the East Harlem (or Spanish Harlem) community is a high concentration of minority (Black and Puerto Rican) residents. East Harlem has been the site of a bilingual, bicultural Puerto Rican community for almost half a century. The cultural and linguistic differences between this group and the majority population influence health attitudes and behavior which, in turn, require a very special responsiveness on the part of The Mount Sinai Medical Center if it is to adequately serve the East Harlem community. The purpose of this paper is to review the Puerto Rican participation in the health manpower structure at Mount Sinai Medical Center in the context of Hispanic health manpower nationally. A focus on necessary Hispanic health manpower is a key factor in providing sensitive, responsive health care to the Spanish Harlem community.

The East Harlem and Puerto Rican Community

In 1970, 163,000 persons were residing in East Harlem, 45 percent of whom were of Puerto Rican ethnicity (3). Over the past ten years, there has been a decline in the East Harlem community with the estimated 1980 population being close to 140,000. Puerto Rican census information is not reliable. The Puerto Ricans vary in skin color from white to black and thereby may be

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categorized as Caucasian or Afro-American. Moreover, the method of identification through Spanish surnames does not distinguish the diverse subgroups of Hispanic or Latins in our society. This confusion does not permit accurate identification of Puerto Rican people. However, in East Harlem, the traditional New York City "home" of the Puerto Rican migration since the 1930's, the Hispanic surname identification is more apt to include primarily the Puerto Rican ethnicity.

Being citizens of the United States, Puerto Ricans may travel back and forth between the mainland and the island. The rural areas of Puerto Rico, from which many of the New York City populations have migrated, are vastly different from the inner urban situation. The bicultural bilingual adaptation is severe and results in great stresses psychologically as well as in physical and social parameters.

The emergence of a New York City Hispanic subgroup has resulted in a compounding of the traditional problem facing any immigrant group in the U.S. The "New York Rican" is the result of an incomplete assimilation to a new society. These second generation people are really more New Yorkers than Puerto Ricans, but because of their heritage, they are considered less New Yorkers than most individuals who have also been born in the city. The cultural ties, language and family structures are frequently markedly disparate when compared to a Puerto Rican born and bred in Puerto Rico. These individuals often are the children of agrarian workers who migrated from Puerto Rico in search of unskilled positions in the mainland only to discover that these positions were quickly disappearing. This represents a break in the classical progression: migration of the unskilled laborer, slow assimilation and final acceptance, which has been the rule for massive migrations to the U.S. in the past.

East Harlem has been designated as a medically underserved area according to federal criteria (4). The East Harlem community as a whole suffers essentially the same level of ill health as other predominantly low-income minority populations in the city, such as, increased infant mortality and morbidity. There are higher rates of hepatitis, tuberculosis, venereal diseases and other infectious diseases. A health survey in East Harlem conducted by the Department of Community Medicine (3) revealed high rates of hypertension, diabetes, arthritis and asthma. Within the Puerto Rican population, asthma was especially severe.

Within East Harlem's boundaries the major hospital facilities include The Mount Sinai Medical Center, Metropolitan Hospital, and North General Hospital. The East Harlem District Health Department and various medical clinics, the Boriken Neighborhood Health Center with its satellite clinic at 1199 Plaza, and the HIP-East Harlem Center provide a network of primary care services in addition to the emergency rooms and OPD ambulatory clinics in the aforementioned three hospitals. The more than twenty so-called "Medicaid Mills," scattered throughout the community, provide health care of varying quality. While there are these many primary care and hospital bed resources, the lack of a rational financial and organizational scheme for the delivery of health services promotes overlapping, chaotic and fragmented medical care. This unfortunate health care system problem is characteristic of most of our inner city communities in the U.S. today.

East Harlem community residents are heavy utilizers of Mount Sinai Hospital. In 1980, a point prevalence analysis of emergency room and ambulatory utilization showed that 34 percent of the "users" were from East Harlem. In a special survey conducted over a three day period in May 1980, 40 percent of patients were found to be of Hispanic origin (6).

On a given day, May 8, 1980, the Mount Sinai Hospital had a full hospital bed census of 1,114 of which 163 had Spanish surnames (14.6%) (7). This accounts for most of the Puerto Rican patients, although Hispanic patients with non-Spanish surnames were not included in the total count.

The level of visits to the Mount Sinai OPD facilities documents utilization of medical care that is equal or higher than that found in the general population (8). The number of visits per patient in East Harlem in 1979 was 4.6 per annum. It would appear that "access to care" as measured by visits to a physician per person per year compares favorably with general national data. Even in terms of hospitalization, the number of hospital beds and bed utilization are reasonable for the needs of East Harlem residents when compared with the general U.S. population At Mount Sinai Hospital the average census o 1,000 beds has an almost constant bed occupancy of 100 East Harlem residents (9). Among inpatients, East Harlem residents represent 10 percent of the total number of hospital admissions.

The Puerto Rican Culture and Modern Medicine

Identifying precisely which of the attitudes and behaviors inherent in Puerto Rican culture make it more difficult for Puerto Ricans to acquire responsive and sensitive care is difficult. Some factors are generally acknowledged. One is the use of folk healers or "espiritistas" (curanderos), especially for the treatment of psychosocial health problems (10), that may result in underuse of the institution-based mental health care system. Reliance on folk healers may be the only viable alternative, however, when one considers the dearth of Hispanic mental health workers.

Another important difference in Puerto Rican health practices relates to the use of the "botanicas," herbal pharmacies. The "botanicas" may be viewed as a prevogue version of the "natural food and vitamin" emporia that have mushroomed throughout the U.S. It is not known exactly how effective are the herbal concoctions available in the "botanicas."

Other important features of the Puerto Rican culture are the strong family unity and the dominance of males. These can significantly influence attitudes toward such diverse health issues as admission to institutional geriatric care, communication between health professionals and family members, as well as family planning and contraceptive procedures.

The Puerto Rican family remains a strong and vital force in the East Harlem community. The solidarity of the family can be threatening to clinicians. It is quite consistent with Hispanic tradition to have the entire family accompany a patient to visit a physician, attend a clinic or visit an inpatient. The number of concerned individuals often exceeds the number permitted by the hospital, and this can create a problem for the hospital staff.

Hispanic Health Manpower Shortfall

The current Hispanic-American health manpower in general is extraordinarily sparse and is not adequate alone to respond to the health care needs and demands of the expanding Hispanic population. The likelihood that the problem will continue at least in the near future is supported by the data in the following table (11).

Note the consistency with which all categories of Hispanic manpower in health fields are in short supply, especially when 20 to 25 percent of the total U.S. society are Hispanic. In the past fifteen years, there have been considerable increases in the numbers of minority group members and also women entering health professional careers. Nevertheless, there are no health professions in which the percentages of Hispanic practitioners or students are equal to their representation in the general population.

Examination of job types of ethnicity at Mount Sinai Medical Center clearly points up the high level (~ 64.8%) of representation of Hispanic employees in lower job ranks and their under representation (1.6%) in the advanced clinical-professional rank (12). An analysis of physicians and faculty members at Mount Sinai Medical Center, as of December 31, 1979, revealed only nine full-time Hispanic physician faculty members—approximately two percent of the entire physician faculty group.

New York City Medical Schools and Hispanic Admissions

Five of the six medical schools in New York City are private and only State University of New York at Downstate is a publicly operated institution. The New York City schools have never achieved the recommended goal of the Association of American Medical Colleges of 12 percent first-year minority admissions. Indeed, New York

TABLE I

Minority Enrollment in Selected Health Professions Schools in the U.S.

	Total Minority	*Spanish Surnamed*
Medicine 1976-77	11.0%	1.6%
Osteopathic Medicine 1976-77	4.4%	0.7%
Dentistry 1976-77	10.1%	1.3%
Optometry 1976-77	7.4%	1.1%
Pharmacy 1976-77	8.9%	1.5%
Podiatry 1976-77	6.1%	0.6%
Veterinary Medicine 1973-74	3.0%	0.5%
Nursing 1974-75	13.6%	3.5%
Diploma	8.4%	2.0%
Associate Degree	16.4%	5.0%
Baccalaureate	14.1%	3.1%

(Adapted from: Minorities and women in the health fields. DHEW Publication No (HRA) 79-22, October 1978.)

City's medical schools averaged 6.9 percent minority admissions in 1976, far less than the 8.9 percent achieved nationally the same year (13). Mount Sinai School of Medicine has had a more adequate record, averaging a 10.2 percent minority admission rate between 1969 and 1976, exceeding the AAMC recommendation for minority admission in 1972 (13.0%) and 1976 (12.3%). The Biomedical Program of the City University of New York–City College of New York has a freshman class, 22 percent of which are Black and Hispanic. Of the 778 M.D.'s who graduated from Mount Sinai School of Medicine between 1970 and 1980, 16 (2%) were of Puerto Rican ethnicity.

The total number of medical students enrolled in U.S. medical schools for the 1979-80 academic year was 63,800 of whom 283 were identified as mainland Puerto Ricans, a mere 0.4 percent of the total medical student body (14). However, if one includes the 700 Puerto Rican students in the Commonwealth of Puerto Rico as well as other Hispanic students, Hispanic students (2,231) represented 3.9 percent of the total U.S. medical student enrollment.

Thus, if viewed from a national perspective, Mount Sinai has had a respectable level of success in recruiting Hispanic and, particularly, Puerto Rican, students.

Nurses

In 1977, 1.4% of registered nurses in the U.S. were Hispanic. Minorities accounted for 6.2% of the U.S. total (15). In New York State in 1977, 1.2% of registered nurses were Hispanic (16). In the summer of 1978, approximately 200 nurses were hired at Mount Sinai. Most were young, unmarried, female B.S.R.N.'s with no prior experience. Six of the nurses (3%) were Hispanic (17).

In light of the estimate that 15 percent of inpatients at Mount Sinai Hospital are of Puerto Rican or other Hispanic ethnicity, three percent Hispanic representation in the nursing workforce represents a significant shortage. The situation is even more serious in the Ambulatory Care Division in which 40% of all patients seen are of Hispanic ethnicity (7).

Medical Social Workers

In the U.S. in general, covering the period of 1969-1974, 42,484 individuals graduated from M.S.W. programs. Of these 1,681 (4%) were of Hispanic origin (18). The Mount Sinai Medical Center has a total of 93 social service staff of whom 13 are Hispanic, and of those 13, 11 are of Puerto Rican ethnicity (19). Given the high number of Puerto Rican health service consumers and the enormous burden of social health problems in this population, the deficiency in this health manpower category is significant. The CUNY affiliated social work academic program at Hunter College with its 1980 enrollment of 541 students has 33 Puerto Rican students of the 45 classified as Hispanics (19).

Mental Health Workers

There is very little epidemiologic data that would document the incidence or prevalence of mental health problems among Hispanics in general or Puerto Ricans in particular. These problems need to be carefully studied before frequency patterns in mental disorders among Hispanic groups or subgroups can be implied. However, if Hispanic mental health needs are at the same level as those of the general U.S. population, the shortfall in Hispanic mental health professionals in all categories is an important concern (18).

Alternative Remedies for the Hispanic Health Manpower Crisis

In the long run, there can be no effective solution to the shortage of Hispanic-American health manpower other than intensive recruiting of Hispanic students into the health field. Among the barriers to this approach are the serious poverty and resulting poor educational opportunities with which many Hispanics must contend, as attitudes and expectations of minority group members create formidable barriers as well. For Mount Sinai School of Medicine and The Mount Sinai Hospital, continued efforts to recruit Puerto Rican students and health manpower should have a high priority. A number of programs have been instituted to enhance Mount Sinai's ability to provide optimum care to people from all social and cultural levels.

The Department of Social Work has developed an effective "ombudsman" (social health advocate) program that employs three Hispanic community health workers to assist patients who encounter problems at the Medical Center. This program has helped to improve the sensitivity of services rendered.

In addition to these measures, Puerto Rican representation on the Hospital's Community Advisory Board and on the Medical Center's Board of Trustees provide direct input into policy making for the institution.

In an effort to upgrade the hospital's ability to communicate with its Puerto Rican patient constituency, several key positions in the hospital hierarchy have been filled with all ethnic groups including Puerto Rican professionals.

A persistant problem encountered by minority admissions programs is a high level of postadmission failure and dropping-out as a result of inadequate preparation and/or social pressures. Mount Sinai School of Medicine provides a supplemental academic program for incoming freshmen minority students. This course is aimed at strengthening their basic science knowledge and the problem solving skills required to cope successfully with the rigors of the basic science curriculum. After an initial full-time summer program the course continues throughout the academic year. Not only does this course shore up academic competency but it creates an important social linkage and support system for minority students.

A community oriented program in the Adolescent Clinic at Mount Sinai Hospital has been designed to provide health services to adolescents from the East Harlem population. Of the total registration of 7,395 adolescents, there is a large group from Puerto Rican families. Based on a two percent sample of the clinic population, Hispanics comprise 54 percent, blacks 44 percent, and others two percent of this population.

In 1968 with the establishment of the Department of Community Medicine, technical assistance and model building projects in health care services were initiated by this academic department. These programs have been presented in detail elsewhere (20–26), so that only a listing of these programs will serve to fill in the picture of Mount Sinai Medical Center's involvement and participation in the delivery of health care in the East Harlem setting.

Briefly, the first Community Medicine venture was to participate in the founding of the East Harlem Health Council in 1968. This organization, although supplanted by the Health Systems Agency District Board G, was the pioneering consumer provider forum to discuss health problems. A member of the faculty in Community Medicine has had a constant presence in this community-based health organization.

In 1970, the Johnson health survey was completed by the Department of Community Medicine and full details of the data were made available in the format of a handbook, The People of East Harlem (3). This useful source of health data was distributed to East Harlem health care institutions and organizations through the generosity of a Commonwealth Fund grant. This data base has been a significant health information resource to many local organizations preparing project grants in the health field.

In 1970, the Wagner Child Health Program was established through a joint New York City Health Department and Community Medicine effort. Although it proved to be a successful comprehensive health care program for the "under five's," model cities funding was withdrawn because of cutbacks that finally dismantled all model cities' projects. This led to a request by the East Harlem Tenants Council, now known as the East Harlem Council for Human Services (EHCHS), to have the Department of Community Medicine provide technical assistance to apply to the Department of Health, Education and Welfare for a neighborhood health center providing health care for a large segment of the East Harlem community. This project was successful and today this neighborhood health center, sponsored by a Puerto Rican led community organization (EHCHS), has a registration of 10,000 as well as a satellite clinic in the 1199 union housing project.

Other Department of Community Medicine technical assistance projects directed to the East Harlem population with special emphasis on minority manpower needs include the Environmental Extension Agent Program (23), the Union 1199–HMO study in East Harlem (24), and the training of community health workers (25). The multidisciplinary health planning team in Community Medicine includes several Hispanic health professionals who are quite familiar with the cross-cultural and bilingual problems in delivering high quality care to the Puerto Rican population.

A particularly complex undertaking was the development of a high school program oriented toward the training of students in health careers. High school students in East Harlem attending the Benjamin Franklin High School were recruited into the SHOP (Student Health Opportunities Program) program to stimulate interest in completing high school, attending college, and entering a health profession (26). This project has undergone considerable modification since its inception in the Department of Community Medicine and it is now administered through the Office of the Dean. Today, students from various high schools are enrolled in special programs to continue the motivation of students for health career development. Over the years there has been representation from all minorities including Puerto Ricans.

Summary

The Mount Sinai Medical Center is pledged to providing responsive, sensitive, high-quality care

to the many diverse community or population groups in New York City. The Hispanic population—which is rapidly increasing throughout the nation as well as in the metropolitan area—represents a major patient population that The Mount Sinai Medical Center must serve.

This paper reviews the special health problems that the Hispanic people in general and New York Puerto Ricans in particular face in our health care system. The bicultural and bilingual issues that influence the pattern of health and disease as well as the health care delivery system requirements are reviewed. The major problems of finding Hispanic health manpower to respond to the health care needs of Hispanic people locally as well as nationally are discussed.

The Mount Sinai Medical Center has shown considerable concern for participation in the solution of the health problems of the Hispanic population. In addition to manpower recruitment policies and training programs, a series of special projects have been established that enhance the ability of the institution to provide high quality clinical care to the Hispanic (Puerto Rican) population.

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Lay Attitudes Toward Physicians and Medical Technology

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Abstract

Increasing government involvement and control of new medical technology, and the current debate about national health care, highlight the importance of lay attitudes toward health services and physicians.

1,458 subjects were sampled in New York City, and completed a ten-item questionnaire about their attitudes and anxieties regarding new medical technology, physicians, and physician training.

Despite recent propaganda against physicians and increasing medical costs, respondents overwhelmingly stand behind their physicians. In addition, new medical technology was heavily favored. Men favored technology more than women. Respondents who were better educated tended to agree with the need for growth in medical technology.

The past five years have seen much more government involvement and control in the distribution and purchase of large new items of medical equipment. The current national debate about national health care shows that this trend will probably increase in coming years. Attitudes of patients toward physicians and health services in general are also of interest to those who study the growth of consumerism as a social movement in the delivery of health services. Most of the investigators in this field have generally focused their attention on sociodemographic and health related factors and characteristics of patients such as age, sex and social class, family size and illness behavior. (1–7).

Time magazine of May 28, 1979 had on its cover a major story about medical expenses and, on the inside, it had a photo of a CAT scanner and several other new pieces of new medical technology, with the title "Those expensive new toys." Obviously attitudes like this convey themselves to the public. This paper samples lay citizens' attitudes toward physicians and new medical technology.

Population

In New York City, 1,458 subjects were sampled in an area of midtown Manhattan near a concentration of medical facilities, including doctor's offices, teaching hospitals, and private clinics. The respondents included 962 women and 496 men. Ages ranged from 18–71 years, with a mean age of 37. Forty-five percent were married, 43% single, and 12% divorced. Thirty-seven percent had graduated high school, 54% had graduated college and 9% had graduate school education.

Method

A ten-item questionnaire with a five-choice range from "strongly agree" to "strongly disagree" was used. Areas covered were attitudes and anxieties about new medical techniques, faith in one's physician, and physician training.

Results

Men generally favored technology more than women, and the more highly educated the respondent, the more likely was a response favoring new technology. Also, oddly, the youngest (18–29 years) and the oldest (50 plus) favored innovation, while the 30–50 age group were reluctant to endorse medical technologic development.

The total population generally "strongly agreed" and "agreed" that they preferred new medical techniques by 69%, with males registering 75% and females 65%.

As seen in Table I, all groups in the population heavily favor new medical techniques; men lead women by a significant difference.

From the Department of Radiology, The Mount Sinai Medical Center, and from *New York Medical College, and **New York University.

TABLE I
"I Prefer New Medical Techniques"

	Total %	Male %	Female %	% High School	% College, Grad School
Strongly Agree	28.2	31.3	26.0	24.7	30.0
Agree	40.3	43.6	39.2	40.2	41.0
Not Sure	24.5	18.4	27.7	26.4	24.0
Disagree	4.3	3.9	5.6	6.3	3.0
Strongly Disagree	2.7	2.8	1.5	2.4	2.0

TABLE II
"I Worry About New Machines"

	Total %	Male %	Female %	% High School	% College, Grad School
Strongly Agree	18.2	10.1	7.4	8.3	9.0
Agree	24.9	20.1	27.8	26.7	26.0
Not Sure	17.2	20.1	29.3	23.6	24.0
Disagree	32.5	39.1	29.1	35.1	33.6
Strongly Disagree	7.2	10.6	6.4	6.3	7.4

As can be seen above, men worry significantly less than women about new technology, and while the response by education was not significantly different statistically, they do indicate the general trend of educated people being less anxious about new medical innovations in general (Table II).

Here again, we see men expressing approval more than women by scores of 67% to 62%, respectively. Quite apart from the medical efficacy of new technology, one begins to see men's greater interest in gadgetry (Table III).

The total score for "strongly agree" and "agree" showed that 59% of men and 70% of women agreed, though there is a significant difference between them. Women seem to conform better and to follow doctor's orders more readily (Table IV). Much has been written of men's denial of needs in terms of admitting weakness. In addition, we see here a more competitive stance from men contrasted to a more compliant one by the female respondents.

This item relates of course to the increasing role of technology and to what extent it may be

TABLE III
"New Medical Inventions are Wonderful"

	Total %	Male %	Female %	% High School	% College, Grad School
Strongly Agree	29.5	35.2	25.0	28.7	28.1
Agree	39.9	31.8	36.6	43.7	38.1
Not Sure	26.7	28.5	30.7	22.4	29.5
Disagree	2.9	2.8	5.0	2.9	3.1
Strongly Disagree	1.0	1.7	2.7	2.3	1.2

TABLE IV
"If My Doctor Says a Test is Necessary I Have It"

	Total %	Male %	Female %	% High School	% College, Grad School
Strongly Agree	24.7	20.1	26.7	28.2	20.1
Agree	41.6	39.1	43.2	43.1	40.6
Not Sure	16.7	19.0	15.5	14.4	17.8
Disagree	12.7	17.6	9.9	9.4	16.1
Strongly Disagree	4.3	4.2	4.7	4.9	5.4

making medical practice less personal. Surprisingly, this question resulted in a large number of "not sures" in all groups, with a high score of 38% for college and graduate school respondents. Men and women "disagreed" and "strongly disagreed" with insignificant differences of scores of 41% and 43%, respectively. Only a minority of the total population, 26.4%, "agreed" or "strongly agreed" that medical practice is still personal (Table V).

Along with new medical inventions come physicians trained in the newest techniques (Table VI). Does it in the view of the public mean that they are also globally better trained? Here, we found "strong agreement" and "agreement" for the total population score of 59%, with men's scores 63% and women's 57%, a significant difference. The general consensus here quite obviously is that physicians are better trained.

This is a question that goes right to the heart of this paper. Do all the new medical inventions and technology, along with the supporting cast of necessary technicians, get between doctor and patient to a degree sufficient to be felt and resented (Table VII)? Here we see that the "agree" and "strongly agree" scores combined showed the total population 42% in agreement, with men 39% and women 45%. Women, more then men, feel the perceived loss of physician contact by a very significant difference. Men who seem somewhat more able to relate to the technical aspects of medicine did not perceive the gap as much in the doctor-patient relationship as did women.

Table VIII was designed to tap feelings of resentment at the increasingly complex technology evolving in medicine. The total population response favors technology. Here we note that by combining the "strongly agree" and "agree" scores, we have only a total of 34% of the population, men 31% and women 37%. Obviously, much of the population does not feel overwhelmed by new machines, and in fact many individuals look to new medical technology for all kinds of wonderful developments.

This question (Table IX) includes a person's attitude towards his physician in the sense of questioning whether the patient's needs are paramount.

TABLE V

"Medical Practice Today Is Still Personal"

	Total %	Male %	Female %	% High School	% College, Grad School
Strongly Agree	7.3	5.7	8.8	8.3	4.9
Agree	19.1	19.6	18.9	16.8	18.0
Not Sure	26.6	30.7	25.5	24.2	38.0
Disagree	29.9	30.5	26.3	32.3	23.7
Strongly Disagree	15.2	10.5	16.5	14.1	13.8

TABLE VI

"Doctors Today are Better Trained"

	Total %	Male %	Female %	% High School	% College, Grad School
Strongly Agree	20.8	22.9	19.9	21.3	20.4
Agree	38.4	39.7	35.8	37.4	40.2
Not Sure	26.7	24.5	29.7	26.9	25.4
Disagree	9.9	9.5	10.1	10.3	10.1
Strongly Disagree	3.1	2.2	3.4	3.4	2.8

TABLE VII

"Technicians and Technology Get Between Doctor and Patient Too Much"

	Total %	Male %	Female %	% High School	% College, Grad School
Strongly Agree	11.9	8.9	14.2	12.6	12.2
Agree	29.8	29.6	30.7	25.3	37.7
Not Sure	29.4	26.7	31.7	32.8	26.3
Disagree	24.7	30.2	20.3	24.7	20.4
Strongly Disagree	3.5	3.9	3.0	4.0	3.1

TABLE VIII
"Complicated Machines Make Me Feel Overwhelmed"

	Total %	Male %	Female %	% High School	% College, Grad School
Strongly Agree	9.1	8.4	9.8	11.5	8.8
Agree	25.1	22.3	27.0	31.6	18.1
Not Sure	23.0	18.3	25.0	24.0	24.3
Disagree	36.0	42.3	32.1	27.4	41.4
Strongly Disagree	6.6	8.4	6.1	5.4	6.9

TABLE IX
"Safety Today Takes Second Place to Technology"

	Total %	Male %	Female %	% High School	% College, Grad School
Strongly Agree	15.4	14.0	15.9	18.7	16.4
Agree	29.4	33.0	28.4	36.5	27.8
Not Sure	22.0	16.8	27.7	17.7	23.9
Disagree	24.2	27.3	20.9	21.4	22.9
Strongly Disagree	9.0	8.9	7.0	4.9	9.0

Here we find, combining "strongly agree" with "agree" scores, that 45% of the population felt that safety takes second place. However, we must also point out that we had another large "not sure" score, 22%. Thus, while 45% said that they agreed that safety took second place, and 22% felt that they weren't sure, we have the beginnings of some question about the patient's role in the medical scheme of things.

In Table X, we find that the "strongly agree" and "agree" scores were a rather surprising 39% for the total population, men 42% and women only 38%. Here again we find that the more educated patient felt that they also requested, or received the best explanation.

Conclusions

Quite obviously, we note that despite the recent increase in propaganda adverse to physicians, and more specifically against increasing medical costs, some important conclusions are reached here. New technology and supposed physician income rise are often cited, but the general public quite solidly stands behind its physicians that is not significantly affected by the intrusion of technology. Scores showed that most patients wanted more personal contact, but also indicated that patients still had a great deal of confidence in their physician. In terms of the expenditures for new medical equipment, by very large numbers the general public responded that they preferred new medical advances, and agreed that technology, and especially new technology, was important in medicine. The results clearly indicate that perhaps the medical profession can move from the position of defensiveness, to a more positive stance in acknowledging the need for both technical development, as well as concern for patients Though men generally tended to indicate less need for dependency on physicians, and to relate to gadgetry better, both men and women felt that medical practice today is of a high quality leve and that they were being treated by bette trained physicians. In general, people who are better educated were more informed, and tended to agree with the need for growth in medica technology.

TABLE X
"My Doctor Explains the Reasons for All Tests"

	Total %	Male %	Female %	% High School	%College, Grad School
Strongly Agree	15.4	19.0	13.5	18.2	16.3
Agree	23.9	22.9	24.7	15.0	27.3
Not Sure	24.2	24.2	23.6	23.7	22.4
Disagree	18.9	20.9	17.2	21.2	18.1
Strongly Disagree	16.9	12.9	20.9	20.8	15.9

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Faculty Development and Resident Training in Epidemiology and Biostatistics

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Abstract

Training programs in epidemiology and biostatistics for physicians whose backgrounds are primarily clinical medicine are not widespread. This paper describes the initial development of such a program which grew out of the needs of an undergraduate course in epidemiology and biostatistics for first-year medical students, and out of a desire to enhance the level of training for residents in preventive medicine. The manpower needs in this first-year course resulted in the development of a teacher-trainee program for our residents in Community Medicine. This program has recently been expanded and now includes a preparatory seminar series for residents and junior faculty in the Department of Community Medicine. In addition, several residents from clinical departments, including Medicine, Pediatrics, and Surgery, have also been attracted to this seminar series and some have further participated as teacher trainees. This program has the potential for becoming a prototype for training clinicians in the areas of epidemiology and biostatistics. The approach to these subjects is substantially different than that found in a school of public health since it addresses issues in clinical decision making and thus may appear more attractive to our clinical colleagues.

During the past decade, the goal of the Department of Community Medicine, Mount Sinai School of Medicine of The City University of New York, has been to develop the capacity of undergraduate medical students and resident physicians to identify and solve health problems in population groups. Since the Department considers epidemiology and biostatistics to constitute the basic sciences of preventive medicine, these subjects are included in the undergraduate curriculum and each resident in community medicine is expected to master the fundamentals of epidemiology and biostatistics early in his/her residency training.

The present format for teaching epidemiology and biostatistics to residents evolved from the need to develop trained teaching assistants for the growing program of undergraduate medical education. Teaching as training has been successful on several fronts: 1) residents have learned the basics of epidemiology and biostatistics and have developed teaching skills; 2) faculty members involved in the program have increased knowledge and skills in both the substantive content and in educational methodology. In addition, the need for high quality faculty to teach the undergraduate course in these subjects has been met.

Background

In 1971, the third year in Mount Sinai's history as a medical school, epidemiology and biostatistics was offered for the first time to first-year medical students under the auspices of the Department of Community Medicine. Since then, the Department has devoted considerable attention to planning and offering the course in ways that would make it accessible, interesting, and stimulating to students. Currently, Community Medicine I: epidemiology and biostatistics is offered as a required 36-hour course during the sec-

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ond half of the first year of the undergraduate program.

The specific curriculum of the course has been described elsewhere (1, 2). The general focus of the course is the application of the principles of epidemiology and biostatistics to clinical problem solving through the critical review of specific articles from clinical literature rather than learning the theoretical underpinnings of epidemiology and biostatistics per se. Thus, the emphasis is far more pragmatic than that found in many schools of public health.

The course is taught largely in a seminar format, with two instructors assigned to each section of undergraduates. In keeping with the focus of the course, each seminar session is devoted to the explication of key concepts and the comparison of two journal articles that illustrate specific principles of research design and/or statistical techniques. Students carry the responsibility for reviewing the articles and presenting their critiques to the seminar group.

Since the initial class at Mount Sinai School of Medicine was small in size (40), the demand for faculty to teach the epidemiology and biostatistics seminars was easily filled by identifying faculty members with appropriate backgrounds who were interested in teaching. Initially, each faculty participant was simply given a course outline and objectives and was expected to teach independently. The approaches taken by individual instructors resulted in a marked disparity among the seminar groups. For example, one instructor pronounced that a paper being reviewed by the class was a classic of its kind, while another attacked the same paper for serious epidemiologic weaknesses. To remedy this untenable situation, faculty meetings were held prior to each seminar session during which a consensus as to the strengths and weaknesses of the papers was developed and the key concepts were reviewed.

Subsequently, the increasing undergraduate population created a need for more teaching personnel. As an immediate response to this need, junior faculty members and then faculty members without specific training in epidemiology and biostatistics were called upon to teach. To assist them in assuming their educational responsibilities, the faculty meetings initially established to reconcile divergent points of view enlarged their commitment to a comprehensive program of faculty development. Through these meetings and a seminar series, senior faculty members helped their junior colleagues to strengthen their knowledge of the substantive content of the course and to develop and use appropriate teaching strategies.

Motivated, in part by the continuing increase in the size of the student population (currently 102 in the first-year class) and in part by the success of the faculty development initiative with junior faculty, it was decided to include residents in preventive medicine as teaching assistants and to designate this role as a formal part of the residency training program. The use of teaching assistants, an integral part of many academic programs, is unusual in preclinical undergraduate medical education. Thus, using residents as teachers in an undergraduate classroom course and structuring this experience as a part of their training are unique features of our approach.

Structure

A preparatory seminar for the teaching assistants is held prior to each undergraduate class session. Initially, these seminars were chaired by a senior faculty person, when the goal was uniformity of instruction; a consensus was reached on how to critique articles and define terms. As training became an additional goal, the teaching assistants have been assigned responsibility for these preparatory seminars. During each seminar, one teaching assistant develops a critique of the papers being reviewed and suggests illustrative teaching materials for the concepts to be covered during each class session. This is presented for discussion in the seminar and in a written form as teaching notes. These teaching notes have been refined and modified each year and form a teachers' handbook, or guide that serves as a starting point for the seminar series.

In keeping with the multidisciplinary nature of the community medicine program, the teaching team consists of a medical and a nonmedical instructor. Nonmedical instructors have represented the full range of disciplines involved with the Department: psychologists, medical sociologists, economists, social workers, as well as persons holding MPH's and DPH's. Each resident has the opportunity to work closely with nonmedical colleagues in the preparatory seminar and in team teaching in the actual class session.

The residents and faculty who have been involved as teaching assistants have expressed the need for more preparation for the teaching role and have requested additional instruction in epidemiology and biostatistics. It is interesting to note that the residents' apparent anxiety about their level of competency is not reflected in feedback from undergraduates taking the course, who generally rated the teaching assistants as being well prepared and as encouraging discussion. In addition, the students' ratings of instructors did not appear to make any distinction between clinical or nonclinical teaching assistants, nor between those with or without prior, more formal, training in epidemiology and biostatistics.

Nonetheless, a special seminar series in epidemiology and biostatistics has been developed for potential teaching assistants and residents from other departments, such as Computer Science, Pediatrics, Medicine, and Surgery, who are interested in training in these areas. It is gratifying to have a request for more training arise from a need on the part of residents rather than being dictated from above. On the whole, the residents are highly motivated to learn the material.

The first cycle of this new seminar series was completed this Spring. All participants were given a pretest and a final examination to assess their learning. In addition to the higher level of epidemiology and biostatistics covered in this course, they were introduced to statistical packages using the computer. The series was well received. The mean scores on the pre- and post-tests were 60.3% and 81.8%, respectively. A total of twenty-nine participated this year and we expect larger enrollments in subsequent years.

This model of teacher-training, apparently attractive to residents in preventive medicine, has the potential of being expanded to include other clinical department residency programs. It is our hope that the expansion of this program will attract interested residents and junior faculty from other clinical departments and thus may serve to strengthen the linkage between epidemiologic insights and clinical practice.

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An Epidemiologic Study of Ski Injuries: Vail, Colorado

Barry Jaffin, M.D.

Abstract

Skiing is one of the most rapidly growing participant sports in the world. Despite advances in the reliability and safety of the equipment, the injury rate remains the same. This study was designed to focus on the "holiday skier." Specifically, how do injured skiers differ from noninjured skiers, and what are the common denominators among these injured skiers. All reported ski injuries during a two-week interval from December 26 through January 8, 1980 in Vail, Colorado were evaluated. 194 reported to the Vail Medical Center emergency room and 305 reported to the clinic yielding an overall accident rate of 3.34 injured skiers per 1000 skier days from a population of 149,300 skiers.

A questionnaire was administered to the injured group seen in the Emergency room and results compared to a randomly selected "at risk" population. This injured group significantly tended to be younger, female and less experienced. Lower extremity injuries outnumbered upper extremity injuries two to one, yet this varied with ability. The odds-ratio were calculated for the sex, age, and ability of the skier and specific recommendations were formulated for high risk groups.

Introduction

"Skiing is one of the most rapidly growing participant sports in the world, and the rising number of injured skiers has become a concern both to the medical profession and to the ski industry itself" (1). This statement, written over 18 years ago still reflects a major health problem, for the incidence of ski injuries has not changed despite advances in reliability and safety of the equipment (2–5) while the site of injury has changed from a distal to a more proximal location on the extremity (6–7).

As of 1977, the skiing population was estimated at five million with a 10–15 percent increase yearly (4). Many investigators have tried to elucidate variables responsible for an annual injury rate of two to ten per thousand skier days accounting for 150–500,000 injuries per year, 80 percent orthopedic in nature (8). However, most investigators have lacked the proper control studies. Only a handful have conducted proper studies on how the injured and noninjured population differ; that is, the number of hours of ski instruction (9, 10), the amount of vertical feet skied per hour (11), and the equipment (12).

This study delves further into the question of how these two populations differ and specifically focuses on the "Christmas-New Year's" week, a time period that contains a great number of vacationing skiers. The variables studied are the sex, age, ability, ski length, height and weight of the skier, the number of release mechanisms of the binding, the use of antifriction devices, the lighting and ski conditions at the time of the accident, the slope difficulty, the number of runs taken before the accident, the ownership of equipment, the date the bindings were last adjusted, the value of morning stretch exercises, the previous injury rate, and the number of days skied during the present season.

Setting

Vail, Colorado is the largest single mountain ski complex in North America and more than 70% of its skier population lives outside of Colorado. The area has an uphill lift capacity of 21,430 skiers per hour, a vertical drop of 3,050 feet, and 57

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miles of trails. The next closest medical center is located in Glenwood springs, 60 miles away, hence all serious injuries are reported to the Vail Medical Center.

Materials and Methods

A questionnaire was designed to evaluate several variables involved in ski injuries (Fig. 1). The questionnaire was completed for all ski-related injuries that presented to the emergency room (E.R.) from 8:30 to 5:00 pm. (On two days, [December 30–31] a modified questionnaire was utilized to poll the "at risk" skier as he or she parked the car. These two middle days were chosen since the skier on these days represented the type of skier that was seen throughout the study.) This accounted for 194 injured skiers, most of whom were brought by toboggan under the supervision of the safety patrol. Injured skiers not requiring this aid could either report to the emergency room by themselves (if immediate aid was required) or to the clinic located in the same building. Since a 24-hour questionnaire service was unavailable, the sex and medical diagnosis were noted for all ski-related injuries occurring

SKI QUESTIONNAIRE

TIME OF ACCIDENT: ______________________

DATE:* ______________________

NAME:* ______________________

AGE: * ______________________

SEX: * MALE FEMALE

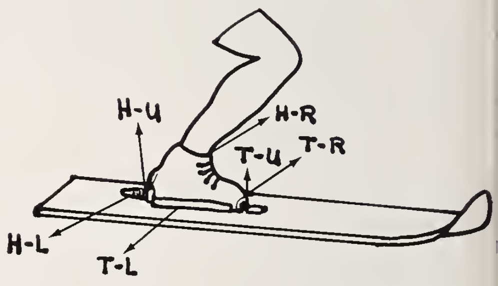
SKI ABILITY:* 1) BEGINNER
2) INTERMEDIATE
3) EXPERT

NUMBER OF YEARS SKIING:* ____________

HEIGHT:*____________ WEIGHT:* ____________

LENGTH OF SKI:* ______________________

TOTAL NUMBER OF RELEASE POINTS OF BINDING: (circle all that apply)*



Toe-Right	Heel-Right
Toe-Left	Heel-Left
Toe-up	Heel-Up

ARE SKIS EQUIPPED WITH ANTI-FRICTION DEVICE:*
YES NO

WHEN WERE BINDINGS LAST ADJUSTED BY SKI SHOP OR EQUIVALENT SERVICE:* ____________

LIGHT CONDITIONS AT TIME OF ACCIDENT:

____

SKI CONDITIONS AT LOCATION OF ACCIDENT:

____

NUMBER OF DAYS SKIED THIS SEASON:* ____________

DIFFICULTY OF SLOPE WHICH YOU WERE SKIING AT TIME OF ACCIDENT:
1) BEGINNER
2) INTERMEDIATE
3) EXPERT

NUMBER OF SKI RUNS BEFORE ACCIDENT OCCURRE

____

WERE STRETCH EXERCISES DONE BEFORE THE DA OF THE ACCIDENT: *
No Yes (how many min.)

DO YOU OWN YOUR SKIS OR RENT THEM?*
Own Rent

DID BINDINGS RELEASE WHEN ACCIDENT OCCURRE
No Yes

HAVE YOU HAD A PREVIOUS SKI INJURY:*
No Yes, (# and type)

MEDICAL DIAGNOSIS

____

* Modified QUESTIONNAIRE

after 5:00 by the E.R. clerk. During the day, those less severely injured were seen in the clinic and noted for their medical diagnosis and sex, hence a total injury rate could be calculated. Three hundred and five skiers compose these two groups.

The data on the control (noninjured) skier population was obtained both from the Vail Associates Research Study and from a modified questionnaire used to randomly poll skiers (N = 233) as they parked their cars. The capacity of each lot (lot "A" = 900, lot "B" = 800 cars) was taken into account so that a proportionate number of skiers could be polled.

The Vail study verifies the representativeness of the parking lot study for there were no significant differences between the sex, age and ski ability of these two populations. The latter group (parking lot) will serve as the "control" population since more information was obtained from them. The Vail Associates Study randomly polled skiers as they waited for the ski lift taking into account such factors as the number of lifts and the lift capacity. The data covered from December 11, 1979 through January 16, 1979, an interval which contained a similar type of skier, the vacationing skier. Two hundred skiers were polled in this manner.

Results

During the two-week interval of December 26 through January 8, 1980, 499 skiers from a population of 149,300 skiers (number of lift tickets sold in two weeks, including the number of season passes used during this time period) sustained 549 injuries yielding a reported injury rate of 3.68 injuries per 1000 skier days. This rate is on the lower side of those reported by many investigators. This value includes those skiers brought down by toboggan, those that walked into the emergency room, and those seen in the medical clinic. The following results are subdivided into the variables investigated and concern the 194 skiers seen in the emergency room except when noted. The variables discussed are those that are most commonly cited in the literature, that is, demographic factors, ski ability, and characteristics of the injury. Table I summarizes the age, sex, and ability of the injured and control populations and states their respective odds-ratio of sustaining an injury. Table II characterizes the type of injury with respect to sex.

Sex: The sex distribution of those injured was significantly different from those not injured ($p. < .01$). Among all injured skiers (N = 499) the accident rate for males was 2.88 injuries per 1000 skier days while females sustained 5.35 injuries per 1000 skier days. When examining the emergency room population, the odds-ratio of sustaining an injury was 4.7 times greater for females than males. When ability was taken into account, females still had an increase risk of injury but this decreased with increasing ability (Table I). When age was accounted for, only those women over 20 years of age had an increased odds-ratio of sustaining an injury compared to men. Among the various types of injuries sustained, women had a significant number of lower extremity (LE) rather than upper extremity (UE) injuries than men ($p. = .02$). This is largely accounted for by the large number of females sustaining sprains to the knee ($p. < .01$).

Age: Youngsters (under age 20) were more heavily represented ($p. < .01$) in the injured group than in the comparison population, whereas age groups 20−39 were under represented. In each age category of males, there was no difference among injured and noninjured with respect to ability level. However, among females, there was a significant difference of ability in the under 20 age group of injured skiers. Most in this group were beginners ($p. < .05$). There were no significant differences among the types of injuries sustained by the younger as compared to the older group.

Ability: There was a highly significant difference of injured vs. noninjured skiers with respect to ability ($p. < .001$) (Table I). Except for females under 20, there was no difference of ability found between the injured and noninjured female skier; young injured females tended to be beginners. Among intermediate male skiers there was a significant difference with respect to age. A large number of the "over 30" group were injured, whereas a highly significant number of intermediates in their twenties did not sustain injury. ($p. < .02$) There was no significant difference seen between the type of injury sustained and the ability groups. However, trends can be seen on Table III. Within each injured ability group, there was no significant age difference between males and females.

Snow Conditions/Visibility: Contrary to the report of Johnson et al (13), the type of injury sustained did not appear to be related either to snow condition or visibility.

Fatigue factor: This variable was measured both by the number of runs taken before the accident and by the time of day when the accident occurred. With respect to the former, there was no

TABLE I

Characteristics of Injured and Control Population

	(N = 194) INJURED SKIERS	(N = 233) NON INJURED SKIERS	ODDS RATIO
SEX			
Males	101 (52%)	164 (70.3%)	.456
Females	93 (48%)	69 (29.6%)	2.180
ABILITY			
Beginners	*63 (32.5%)*	*16 (6.9%)*	*6.50*
Males	24	10	0.369
Females	39	6	2.70
Intermediates	*83 (42.8%)*	*152 (65.2%)*	*0.398*
Males	40	103	0.442
Females	43	49	2.25
Experts	*48 (24.7%)*	*65 (27.9%)*	*0.85*
Males	39	51	0.84
Females	9	14	1.18
AGE			
Under 20	*71 (36.6%)*	*25 (10.7%)*	*4.80*
Males	39	9	2.16
Females	32	16	0.46
20-29	*61 (31.4%)*	*108 (46.4%)*	*0.53*
Males	33	77	0.474
Females	28	31	2.10
30-39	*16 (8.2%)*	*50 (21.5%)*	*0.33*
Males	6	28	0.47
Females	10	22	2.12
40-49	*35 (18.0%)*	*36 (15.5%)*	*1.20*
Males	21	30	0.30
Females	14	6	3.30
50-59	*10 (5.15%)*	*11 (4.72%)*	*1.10*
Males	3	10	0.04
Females	7	1	23.00
60-69	*1 (0.52%)*	*3 (1.29%)*	

significant difference seen among the sex, age, or ability of the injured skier. 16% of the injured skiers hurt themselves on the first run, 11.3% on the second, 15.5% on the third, 20.1% on the fourth, 13.4% on the fifth. With the latter, there was similarly no significant difference regarding age, ability, or sex. Had skiers with less severe injuries (those seen in the clinic) been included, more skiers would have been shown to report their injuries later in the afternoon.

Difficulty of Slope Where Accident Occured: Almost all subgroups of injured skiers, except female beginners and female experts hurt themselves on slopes equal to their stated ability. The former group sustained injuries on more difficult slopes (p. < .05) whereas the latter hurt themselves on easier slopes (p. < .01).

Effect of Binding Release on Upper and Lower Extremity Injuries: Among LE injuries, there was no significant difference seen with ease of binding release with respect to sex, ability level, rental vs own equipment, and snow conditions, although as the ability of a skier increased, the rate of release increased (Beginners: 29.6%, Intermediates 40.6%, Experts: 45.4%). Males tended to release out of the bindings more than females (46.6% 29.4%). Rentals, taking into account sex and ability had release rates comparable to those o females, a rate which is quite low (30%).

Discussion

An important aspect in determining how the injured population differed from the noninjured was the establishment of a representative "a risk" population so that appropriate conclusion

TABLE II

Types of Injuries Seen in Emergency Room (206 Injuries, 194 Skiers)

UPPER EXTREMITY:	MALE	FEMALE	TOTAL
Head			
Concussions	3	2	5
Fractures			
Ribs	1	0	
Clavical	0	1	
Humerus	2	0	
Ulner	1	0	10
Radius	1	0	
Wrist	1	1	
Thumb	2	0	
	(8)	(2)	
Dislocations			
Acromial-Clavicular Separations	4	2	18
Shoulder	8	4	
	(12)	(6)	
Sprains			
Cervical	0	1	
Lumbosacral	4	2	13
Ulnar-Coll. Lig.	1	3	
Rotator Cuff	1	1	
	(6)	(7)	
Contusions			
Shoulder	3	2	
Elbow	2	0	9
Rib	2	0	
	(7)	(2)	
Lacerations			
Scalp	3	1	
Facial	6	3	14
Finger	1	0	
	(10)	(4)	
SUBTOTAL	46	23	69

LOWER EXTREMITY	MALES	FEMALES	TOTALS
Fracture			
Femur	2	0	
Tib-Fib	4	5	
Tibia	4	2	27
Fibula	5	1	
Ankle (Malleolus)	1	3	
	(16)	(11)	
Sprains			
Knee-"mild"	14	19	
Medial Col. lig	9	21	
Anterior Cruciate	1	6	89
Lateral Collateral	1	1	
Ankle	7	7	
Torn Meniscus	3	0	
	(35)	(54)	
Contusions			
Tibial	3	2	
Sacral	1	2	
Gastroe	4	2	19
Hamstring	4	1	
	(12)	(7)	
Lacerations			
Leg	0	1	
Scrotal	1	0	2
	(1)	(1)	
TOTAL	110	96	206

could be drawn. The "at risk" population obtained from Vail Associates from the interval of December 11 through January 16, 1979 matched the parking lot poll "at risk" skier with respect to sex, age, and ability thereby giving substance to the representativeness of the control population. Analysis was performed on the injured 194 skiers.

Most accidents occurred in the afternoon, although fatigue did not seem to play a major role, for there was no significant difference accounting for age, sex, and ability among the number of injured skiers regarding the time of the fall, and the number of runs taken before the accident. However, as stated by Haddon et al (5), more skiers ski in the afternoon and thus account for the increased number of accident seen in the late day.

The ability of the skier appeared to be an important factor in determining the likelihood of sustaining an injury, for beginners had the highest odds-ratio of injury (Table I). It is important to note that the accident rate can not be accurately determined for the various ability groups since the ability group of those injured were only known for 38% of the injured population (the E.R. population N = 194). It can not be assumed that the percentage within each ability group were the same for the other 62% (clinic population N = 305) since these injuries were less severe and are subject to the biases of reporting (14). The type of injury varied with ability as noted by Table III. Fractures, contusions, lacerations, and dislocations proportionately increased as the skier's ability level increased. There were relatively more LE injuries among beginners and intermediates, while relatively more UE injuries among experts.

Sex per se did appear to be a major factor in

TABLE III

Site of Injury vs. Ability

LOCATION $\left(\frac{UE}{LE}\right)$		BEGINNER $\left(\frac{13}{53}\right)$	INTERMEDIATE $\left(\frac{25}{59}\right)$	EXPERT $\left(\frac{31}{25}\right)$
Fractures	$\left(\frac{11}{26}\right)$	10 (15.2%)	16 (19.0%)	11 (19.6%)
Sprains/ Strains	$\left(\frac{11}{91}\right)$	42 (63.6%)	42 (50.0%)	18 (32.1%)
Contusions	$\left(\frac{10}{18}\right)$	8 (12.1%)	11 (13.0%)	9 (16.0%)
Lacerations	$\left(\frac{14}{2}\right)$	2 (3.0%)	6 (7.1%)	8 (14.3%)
Dislocations	$\left(\frac{18}{0}\right)$	3 (4.5%)	8 (9.5%)	7 (12.5%)
Misc.	$\left(\frac{5}{0}\right)$	1 (1.5%)	1 (1.2%)	3 (5.4%)
(TOTAL)	$\frac{69}{137}$	66 (99.9%)	84 (99.8%)	56 (99.9%)

(Misc., Head concussion)

determining the injury. Women, when controlling for ability and age greater than twenty, had increased risks of injury as compared to men (Table I). Although the type of injury varied with gender, males (controlling for ability) sustained proportionately more fractures, contusions, lacerations, and dislocations than females. The latter sustained more sprains and strains to the knee. Males and females both had more LE than UE injuries (Table II).

Younger skiers (under 20) appeared to have a greater risk of injury when compared to the other age groups. It is of importance that this group was not over represented by beginners for the subdivisions were as follows: 39.4% beginners, 40.8% intermediate, 19.7% experts. With respect to sex, 64.4% of the beginners were female whereas 41.3% and 21.4% of the intermediate and experts respectively were female. These figures suggest that age per se is a factor in ski injuries. Within this age group, women sustained more fractures and sprains than did men.

The difficulty of the slope on which the accident occurred in relation to the skiers ability may be explained by the problem of classification. Each skier was initially asked to define his or her skiing ability. Specific criteria were mentioned only when the skier asked, for most skiers quickly responded to the question. The classification system of beginner, intermediate, and expert was presumed to be widely understood by skiers. Perhaps the findings that female beginners hurt themselves on more difficult slopes whereas female expert skiers hurt themselves on easier slopes suggests that females were not consistent in assessing their ability level.

The length of the ski, height and weight of the skier, number of binding release modes, use of an antifriction device, date the binding were last adjusted, number of skiers doing stretch exercises that morning, previous injury rate, and number of days skied this season did not significantly differ between the injured and non-injured skier population with respect to age, sex, and ability.

Among ability levels, beginners sustained the highest percentage of LE injuries (76.6%) and 71.4% of all injured beginners used rental equipment. This does not imply that the use of rentals per se predisposes the skier to an injury. Among LE injuries, rental bindings (controlled for ability) had a release rate of 30.3% while beginners (accounting for ownership of equipment) had a release rate of 29.6%. This suggests that beginners without rentals had a similar release rate thereby illustrating the low release rate for beginners, a factor which might explain the number of LE injuries in this group.

When the clinic population was examined, no significant difference of the sex distribution and type of injury sustained was seen when compared to the E.R. population.

Conclusions

This study illustrates that sex, ability, and age of the skier are important criteria to access injury potential. The young, inexperienced female had the highest risk of injury. Analysis of the 194 injured skiers seen in the emergency room revealed specific subpopulations with various injury risks.

1. Irrespective of sex, lower extremity injuries were more common than upper extremity injuries. Perhaps emphasis placed on preconditioning the leg muscles of the skier through the use of exercises such as cycling, and jogging may decrease the injury rate. Women may need to strengthen the muscles surrounding the knee for they sustained a significant number of knee injuries.

2. With respect to ability level, experts sustained many upper extremity injuries hence this group might benefit by strengthening the shoulder girdle, for dislocations were the most common UE injury. Handball, racketball, tennis, and weight lifting could be recommended.

3. The ski group under 20 years of age had a high risk of injury. This group needs to be told of this fact. Perhaps educating these younger skiers to the "no nonsense" way of skiing would help.

4. Although no control study was done on the rate of binding release on the "at risk" skier, it appears that the release rate is quite low for all injured skiers (Beginners: 29.6%, Intermediates 40.6%, Experts: 45.4%). Perhaps if the release rate were to increase, that is, if skis were made easier to release, fewer lower extremity injuries would occur. However, UE injuries might increase due to premature release. It is of note that the overall injury rate would probably decrease since the number of LE injuries surpass the number of UE injuries 2:1.

This study attempted to elucidate the risk factors involved in ski injuries by comparing "at risk" skiers with injured skiers. A comparison of this type brings forth the major differences seen between the two populations. The study is unique in that it examines a ski population which is not only made up of a great number of vacationing skiers, but investigates a two-week time period which is early in the ski season and thereby decreases the variability of the number of days previously skied by each skier during the 1979-80 ski season. This, in turn, makes the analysis more simple and leads to more appropriate conclusions.

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This study partially fulfills the requirements set forth by the Department of Community Medicine while the author was a third-year student.

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The 18th Bernard H. Eliasberg Memorial Symposium

Bernard H. Eliasberg, M.D.

Introduction

Dr. Bernard H. Eliasberg was associated with The Mount Sinai Hospital for some 56 years. He joined the House Staff in 1906, and was appointed anesthetist in 1910. He and Charles Ellsberg first described insufflation anesthesia as a means of achieving homeostasis during thoracic surgery. He had a long association in the pioneering days of thoracic surgery and by 1923 had become Supervising Anesthetist. He finally became Chief of the Department in 1943, a position that he held for seven years. He remained on the consulting staff until he died in 1962.

Dr. Eliasberg was one of the Founders of The New York Society of Anesthetists which later became the American Society of Anesthesiologists and he was an early diplomate of the American Board of Anesthesiology. He was a fine teacher, a skillful anesthetist, whose opinion was constantly sought by his colleagues. Dr. Eliasberg was one of the vanishing breed of gracious gentlemen of the "old school" and a considerate colleague who was past master at "pouring oil on troubled waters." He was endowed with a deep sense of humor and a tremendous facility as a raconteur and his ability in this regard was frequently sought as an after dinner speaker.

The evil that men do lives on, the good is oft interred with their bones. No evil has been associated with the name of Bernard H. Eliasberg and it is our duty to ensure the good he did is perpetuated for the education of his young and not so young disciples---------"Ne obliviscamus."

From David C. C. Stark, M.D.
Professor and Chairman
Department of Anesthesiology

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Postoperative Hypoxemia

James B. Eisenkraft, M.D.

The value of oxygen therapy during the early postoperative period was recognized over 130 years ago (1) although knowledge regarding its less empiric use has accumulated only recently. Over the past three decades, advances in technology have made measurements of oxygen by physical methods simple and readily available. The many investigations into various aspects of oxygenation have resulted in data which indicate that arterial hypoxemia is an almost inevitable accompaniment of the postoperative state (2, 3).

Understanding the physiology of postoperative hypoxemia requires knowing two terms that are different but are often used synonymously. Hypoxemia refers to a reduction in the oxygen content of the blood (that is, volume of oxygen per unit of volume of blood). Hypoxia refers to a low oxygen tension in the blood (or other tissue). Since oxygen content of blood is a function of hemoglobin concentration, saturation, pH, temperature PO_2, shape and position of the oxygen dissociation curve, the two terms should be used advisedly.

The incidence and severity of postoperative hypoxemia have been associated with various factors.

Age: There is a close correlation between increasing age and degree of postoperative hypoxia. This reflects the inverse relationship between age and arterial PO_2 (PaO_2) in unanesthetized normal subjects, so that it is most severe in those patients least able to tolerate it (4, 5). Arterial PCO_2 ($PaCO_2$), however, remains essentially unchanged with advancing age (6).

Duration and *technique* of anesthesia and *site* of *operation* are also significant. Marshall and Millar (6) observed that following minor procedures when anesthesia lasted less than twenty minutes, there was a tendency for pulmonary overventilation to occur and PaO_2 was normal or slightly elevated. Marshall and Wyche (7), reviewing a number of studies related to postoperative oxygenation, found that general anesthesia administered for nonabdominal operations lasting more than 30 minutes resulted in a reduction of PaO_2 that was maximal immediately following termination of anesthesia and which progressively returned towards normal in a three-hour period. General anesthesia for abdominal procedures was followed by the same initial changes in PaO_2, but with no return towards normal in the first three hours. Reduction of PaO_2 persisted and, in some cases, deteriorated for several days. When epidural anesthesia was employed for abdominal surgery, the PaO_2 did not begin to decrease until several hours after completion of surgery, and then it followed the course of abdominal procedures performed under general anesthesia.

Before considering the physiology of possible causes of postoperative hypoxemia, we should briefly consider the normal cascade of oxygen partial pressures. Oxygen normally flows from the environment down a partial pressure gradient to reach the mitochondria where it is utilized (8). The PO_2 in dry air at sea level is 159 torr. If the air is fully humidified at body temperature when the saturated vapor pressure of water is 47 torr, the inspired PO_2 (the PIO_2) becomes 21% of (760-47) or 147 torr. The inspired gas passes via the airways to the alveoli. The PO_2 in the alveoli (P_AO_2) is a function of oxygen consumption and alveolar ventilation (V_A). There is a partial pressure difference between alveolar (A) and arterial (a) oxygen tensions, the (A-a) O_2 difference. This is caused by a combination of factors including ventilation-perfusion abnormalities, venous admixture, and the physical barrier to diffusion of oxygen across the lung. The tissues are thought to be in equilibrium with venous blood and the arteriovenous oxygen content and tension differences are related to tissue oxygen consumption and to perfusion.

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Postoperative hypoxia may now be considered in reference to the oxygen cascade. For example, the alveolar P_AO_2 may be reduced as a result of decreased inspired oxygen (PIO_2) or as diminished alveolar ventilation (V_A).

Diminished PIO_2 may be caused by failure of an oxygen delivery system or by inert anesthetic gas excretion. Nitrous oxide (N_2O), is an important component of most anesthetic techniques. At the end of the anesthetic, if the patient is switched directly from breathing a N_2O/O_2 mixture to air, N_2O is rapidly excreted into the alveoli. Nitrous oxide is about 30 times more soluble than nitrogen so that the volume of N_2O leaving the blood exceeds the volume of nitrogen entering the blood and this dilutes the oxygen present in the alveoli. This phenomenon is termed diffusion hypoxia or the Fink effect (9, 10). Severe arterial hypoxemia may result but nitrous oxide excretion is completed rapidly and the Fink effect is probably negligible within 30 minutes. High inspired oxygen concentrations are advisable during this transition period, especially in high risk patients.

Alveolar hypoventilation may be considered under several headings:

a) Mechanical impairment to breathing.

b) Increased respiratory dead space.

c) Respiratory depression. The last is probably the most frequent cause of hypoventilation. It may be central (CNS disease, premedicant drugs, anesthetic agents) or peripheral (neuromuscular blocking agents) in origin.

Post-hyperventilation hypoxia falls into the category of a central respiratory depressant phenomenon. Marshall and Millar (5) compared spontaneously breathing anesthetized patients with those who had been paralyzed and hyperventilated so that their arterial PCO_2 was roughly halved during anesthesia. Postoperatively, the fall in arterial P_aO_2 following hyperventilation was double that following spontaneous ventilation. Hypoxia in the former case was thought not to be due to under ventilation because P_aCO_2 was normal or low. However, arterial P_aCO_2 depends upon CO_2 production as well as alveolar ventilation. Hyperventilation depletes the large store of carbon dioxide in the body leading to a reduced output postoperatively so that a normal P_aCO_2 at this time implies that the patient is hypoventilating.

Since the CO_2 tension in the blood is the most important respiratory stimulus, the hyperventilated patient with a low $PaCO_2$ will have little or no respiratory drive until his $PaCO_2$ recovers and exceeds his apneic threshold. The latter may have been increased by anesthetics or respiratory depressant opiates given during the anesthesia.

Opiate induced respiratory depression may now be antagonized by naloxone, a specific narcotic antagonist. Some patients who have received fentanyl, an opiate, in large doses during the anesthesia have been observed to recover ventilation-wise during the first hour postoperatively, but later to develop respiratory depression. Renarcotization following naloxone antagonism has also been observed. A suggested explanation has been that fentanyl is excreted into the stomach where, as a weak base, it ionizes and becomes trapped. It then passes into the small intestine where the change of pH reduces the degree of ionization, the drug is reabsorbed, blood levels rise again and the patient becomes renarcotized and depressed.

Oxygen consumption is the third factor bearing on alveolar P_AO_2. Bay, Nunn and Prys-Roberts (11) found that there was no correlation between oxygen consumption and arterial PaO_2 in ten shivering postoperative patients. In every case ventilation was adequate for the increased metabolic demand of shivering.

Let us now consider arterial PO_2 (PaO_2). If alveolar PO_2 (P_AO_2) is normal but arterial (PaO_2) falls, then there is an increase in the (A-a) oxygen difference. It is well known that the A-a gradient increases during anesthesia and this increase persists into the postoperative period.

Ventilation-perfusion abnormalities result from lung volume changes following anesthesia. Functional residual capacity (FRC), tidal volume and inspiratory reserve volume decrease and positive correlations have been established between A-a gradient and decrease in FRC (7, 12, 13). The etiology of the decrease in FRC is not well understood but its significance in terms of hypoxia is clear cut. It explains the increased incidence of hypoxia in patients who are obese, in pain, or who have abdominal distension. In these instances, FRC is decreased facilitating airway closure and alveolar collapse (14).

Venous admixture and intrapulmonary shunting also contribute to the increase in A-a oxygen difference. Sykes et al (15) have shown that volatile anesthetic agents produce a reversible depression of the pulmonary hypoxic vasoconstrictor (HPV) reflex. This reflex normally diverts pulmonary blood flow away from areas which are poorly ventilated. Depression of the reflex permits perfusion of hypo- or nonventilated areas of lung causing a right to left shunt of varying magnitude. Since volatile anesthetic agents such as halothane and enflurane are excreted for many hours following conclusion of anesthesia, this effect on HPV may contribute to postoperative hypoxemia. Weinreich et al (16) have suggested that intravenous anesthetic agents may be more desirable than volatile agents since the former do not appear to depress hypoxic pulmonary vasoconstriction.

High concentrations of oxygen given during or following anesthesia may produce absorption atelectasis which will exacerbate the degree of venous admixture if ventilation is inadequate.

Does arterial hypoxia (low PaO_2) during the early postoperative period matter?

The most important function is the maintenance of tissue oxygenation and the "oxygen flux." Oxygen flux represents the rate of oxygen availability to the tissues (5).

It is a function of hemoglobin concentration, saturation and affinity for oxygen, and the cardiac output.

$$\begin{aligned}\text{FLUX} &= \text{Cardiac output}\\ &\quad \times \text{arterial } O_2 \text{ saturation}\\ &\quad \times \text{hemoglobin concentration}\\ &\quad \times 1.39^{*}\end{aligned}$$

Substituting normal values for the above,

$$\text{FLUX} = 5000 \text{ ml/min} \times \frac{95}{100} \times \frac{15}{100 \text{ g/ml.}} \times 1.39$$

$$= 1000 \text{ ml/min (approximately) of oxygen}$$

** Since 1 gm Hb combines with 1.39 ml of oxygen when fully saturated.*

To maintain tissue oxygenation, tissue perfusion (cardiac output), hemoglobin concentration and hemoglobin saturation (a function of pH, temperature, 2-3 diphosphoglycerate levels, $PaCO_2$, P_{50}, and especially PaO_2) must be adequate. Deficiencies in one may be compensated to some extent by increases in another. For example, the anemic patient (low hemoglobin concentration) compensates by increasing his cardiac output, thereby maintaining oxygen flux.

Hypoxia (low PaO_2) and hypotension (low cardiac output) should certainly be avoided, especially together in the same patient! If cardiac output or tissue perfusion is low, more oxygen will be extracted from each volume of blood exposed to the tissues. A reduction in mixed venous oxygen content would result. In the study of shivering patients mentioned earlier (11), one patient who had an increased oxygen consumption (1192 ml/min) due to shivering, had a cardiac output (9.4 L/min) which was inadequate for his oxygen consumption so that his arterial/mixed venous oxygen difference was increased (12.7 ml/100 ml).

The above considerations of the physiology of postoperative hypoxemia indicate that in most patients an increase in the inspired oxygen concentration will counteract the tendency to hypoxia. Postoperative patients are therefore routinely given controlled oxygen therapy during this critical recovery period (5, 17). In those patients especially at risk, or in any cases of doubt, measurements of arterial and/or mixed venous blood gases are essential.

Cyanosis may be the first sign of hypoxemia. Before measurements of oxygen were readily available, the diagnosis of hypoxemia was almost invariably made by observation of the patients' appearance. Gross cyanosis is indisputible but mild degrees may be difficult to detect clinically. Patient appearance depends upon lighting and Nunn has investigated the correlation between arterial oxygenation and patient appearance under different lighting conditions (18). His study resulted in recommendations that have been generally adopted in principle, namely that hospital lighting be standardized and that medical and nursing staff be aware of the nature of the lighting installed and its effect on patient appearance.

In conclusion, I have reviewed the physiologic basis of hypoxia that may occur during the immediate postoperative period. Hypoxemia is most likely to occur in those elderly or high risk patients who are least able to withstand it. I hope that an awareness of the mechanisms involved will make us more conscientious in the administration of oxygen to, and the monitoring of, all our patients during this critical period.

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Management of Postoperative Hypertension and Hypotension in the Recovery Room

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The recovery room is an integral part of today's anesthetic and surgical care. It provides an area for close medical and nursing supervision of postoperative patients.

Many (1) of the physiologic disorders that are readily recognized in the fully awake, nonmedicated patient are modified, ablated, or entirely eliminated by residual anesthesia. In the recovery room, this presents major difficulties in recognizing problems such as hypoxia, hypoventilation and hypovolemia.

The key (2) to optimal postoperative management is anticipation, recognition, and immediate action–closely observing and monitoring both the therapy and the progress resulting from therapy.

Control of Blood Pressure

There are two main control mechanisms for adjusting the blood pressure (2). The first is through the autonomic nervous system which responds to acute changes in blood pressure. The second, although poorly understood, operates through the kidney and is involved in situations of prolonged changes in arterial blood pressure. The autonomic nervous system has strategic points in aortic arch and caroted bodies. Cerebral and coronary vessels have a relatively poor sympathetic innervation. They are a little affected by baroreceptor reflexes; thus the drop in blood pressure results in shifting of circulatory blood volume from less vital organs such as muscles, splanchnic areas and skin, to organs such as heart and liver. The autonomic nervous system, by inducing changes in heart rate, peripheral resistance and venous tone, modifies the blood pressure. The humoral system which is involved in prolonged changes in arterial blood pressure can be explained by the renin-angiotensin system. The juxtaglomerular cells of the kidney contain granules that have similar characteristics to renin. When renal blood flow is diminished, the number of these granules decreases (4) and renin is released into the circulation. Renin is a proteolytic enzyme and acts on alpha 2-globulin in plasma to form the decapeptide angiotensin I. Angiotensin I is hydrolyzed in the plasma to the octapeptide angiotensin II. Angiotensin II by itself is a powerful vasoconstrictor.

Any discussion about blood pressure should take in consideration:

$$\text{blood pressure} = \text{cardiac output} \times \text{vascular resistance}.$$

If resistance were always constant, changes in blood pressure would reflect changes in blood flow. Conditions like anesthesia, stress, infection and drugs alter vascular resistance so that blood pressure may be a poor indicator of flow. Also keeping in mind that cardiac output = heart rate × stroke volume, we should ask ourselves every time we manage a blood pressure problem in the recovery room whether we need to treat the central power station or peripheral network. The central area, the heart, will be discussed later. In Figure 1, there is a family of ventricular function curves that change constantly depending on the inotropic state of the heart (5). The use of central venous pressure to make decisions regarding left ventricle function is generally wrong. However, central venous pressure is very useful as a gauge of venous return to the right heart and to the right ventricular performance. There may or may not be any correlation of central venous pressure with left sided filling pressures. It is possible to have left sided filling pressures high enough to

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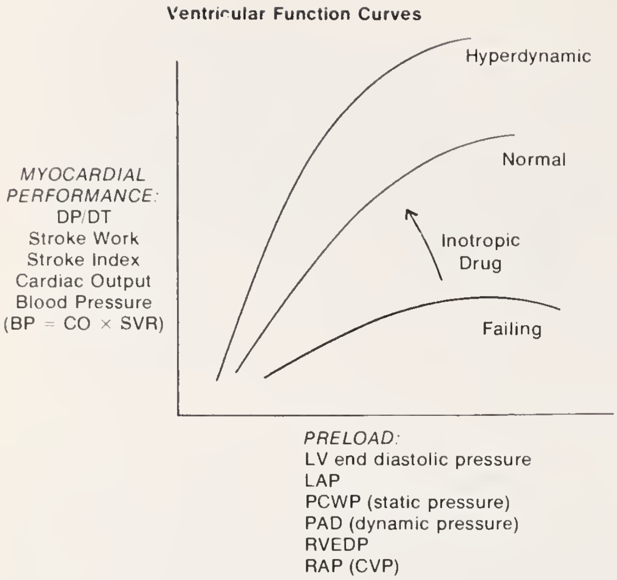

(FIG. 1)

cause pulmonary edema with a normal or low central venous pressure.

Of use in the recovery room are some diagnostic aids, some of them used in every patient and some when you want to be more specific. The diagnostic aids used to diagnose the problem and to evaluate the treatment are:

Hematocrit
Serum electrolytes
Pulse rate
Blood pressure
Urine output
Urine concentration and electrolytes
Central venous pressure
Pulmonary artery pressure
Pulmonary artery capillary wedge pressure
Cardiac output

Hypertension

In managing a patient with hypertension, treatment and manipulations should be aimed at arteriolar level because it presents the biggest resistance. The pressure in these small arteries drops from 95 mm Hg to 35 (6). The biggest determinant of arterial blood pressure is the tone of smooth muscles in the walls of the arterioles. This can be markedly altered by the sympathetic nerve ending that release noradrenaline at their terminals.

When to Treat Postoperative Hypertension?

No absolute figures can be given but most authorities agree that A) if systolic blood pressure is more than 180 and diastolic is more than 120, it is abnormal for the patient or B) a rise of 20% or more than the highest preoperative pressure or C) if there are cardiac or cerebral signs or symptoms, active steps to reduce the arterial blood pressure should be taken.

The exact cause for postoperative hypertension is not always well established. We are talking about catecholamines but we are learning more about renin angiotensin system. Factors influencing development or postoperative hypertension include: advanced age, previous history of hypertension, withdrawal of antihypertensive medications and the type of surgery—major vascular and caroted artery surgery. Factors precipitating postoperative hypertension include: pain, hypercarbia, hypoxia, hypotermia. These factors should be ruled out before treating hypertension.

Goal of Treatment

When to start—when to stop.

In the *Lancet,* April 21, 1979 on p. 861 Steward states "Thus it would seem that in severe middle aged hypertensives attempts at normalization of high blood pressure may precipitate as many infarctions as it prevents. Other cardiovascular complications did not exceed the incidence expected during treatment. The findings suggest that the blood pressure in such patients should seldom be reduced by more than 22% or to diastolic level of 104 to 110 mm Hg.

Treating high normals is still a controversial topic. Treating moderately severe diastolic hypertension is not (8).

Dr. Steward studied 169 moderately severe hypertensives with follow-up time of over six years. Myocardial infarctions were five times more frequent in patients whose blood pressure had been reduced below 90 than in those whose final diastolic blood pressure was 100-109. Dr. Steward is not proposing that we stop treating moderately severe hypertension. The question is how far should hypertensive blood pressure be lowered, that is, reassess end point.

Rationale of Treatment

Figure 2 explains that understanding the morphology and function of the coronary vasculature has given prominence to the role of the subendocardial collateral network (4). When intramural vessels are occluded, the subendocardial collateral system distributes blood flow to the occluded area, but this system may also be subject to occlusion by high intracavitary left ventricular diastolic pressure. Such high pressures usually

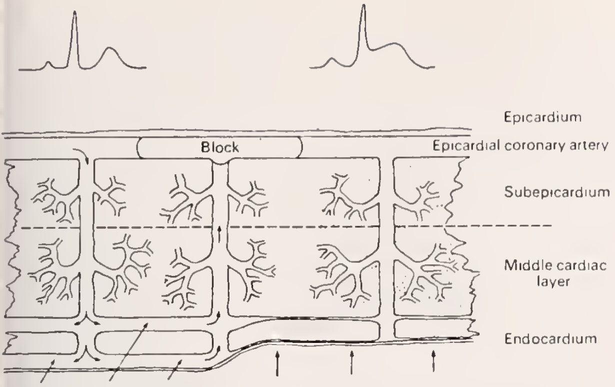

FIG. 2. The subendocardial collateral network

occur when the left ventricle is in a state of acute failure as a result of an increase in systemic vascular resistance—a situation which is particularly common in the patient with severe hypertension. It seems that reduction of the afterload is beneficial in such conditions.

Not every case of hypertension we are dealing with has unclear aetiology. The following conditions can cause hypertensive crisis.

Encephalopathy
Intracranial hemorrhage
Renal failure
Toxemia of pregnancy
Pheochromocytoma
Vasoconstrictor overdose
Thyroid crisis
Paraplegia
Burns

Treatment

The future of hypertension treatment has much promise in renin angiotensin system, calcium blockers and vasodilators.

Arteriolar dilating properties, that reduce mean arterial pressure, may also alter vessel compliance and thus decrease peripheral vascular resistance and blood pressure as well as left ventricular wall tension and oxygen demand. We feel that nitroglycerin (10) may be the preferred vasodilator in patients with coronary artery disease for the following reasons:

1. It is easy to regulate the dose when given in a dilute intravenous solution.
2. Excessive hypotension is rare and recovery is rapid.
3. Minimal increases in heart rate occur
4. It has no known toxicity
5. It increases collateral circulation through the myocardium
6. It redistributes blood flow to the subendocardium and does not produce intracoronary steel.
7. Decrease heart size and wall tension.

In summary, we would treat a patient with hypertension and ischemic heart disease with nitroglycerin and propranolol first. If the patient does not respond, we would use Arfonad, nitroprusside or phentolamine to augment initial medication and resume his preoperative antihypertensives as soon as possible.

Postoperative Hypotension

It is very common and requires immediate investigations. Quickly, before instituting any therapy, the following should be checked:

1. Possible error in blood pressure measurement
2. Miscalibration of a transducer
3. Artifactual measurement due to an improperly placed or sized blood pressure cuff
4. The differential between one extremity and the other

The most common cause of hypotension in the Recovery Room is due to relative or absolute hypovolemia. We can summarize causes of hypotension in the recovery room as:

Unreplaced blood loss
Continued blood loss
Third space
Anesthetic effects
Temperature
Septic shock
Cardiogenic shock

Management of Hypotension in Recovery Room

Look at the history of the patient carefully to assess heart function and decide how much monitoring should the patient have before fluid challenge. A useful test is to administer 250 ml of crystalloid solution over 5-10 minutes and watch for a rise in arterial blood pressure or central venous pressure. If the blood pressure rises without much change in central venous pressure, it suggests that the patient was indeed hypovolemic and additional volume can be given. If central venous pressure rises rapidly with acute volume infusion, it suggests that myocardial depression may be involved in the hypertensive episode. If hypotension persists despite volume therapy, further assessment is necessary. This may include more detailed evaluation of myocardial function and left ventricular filling pressures using a pulmonary artery catheter. Figure 3 shows combinations of right arterial pressure (central venous pressure) with pulmonary occlusive pressures and their interpretations.

Why Do We Use Crystalloids?

The low cost and ready availability of a balanced solution should favor its use with packed

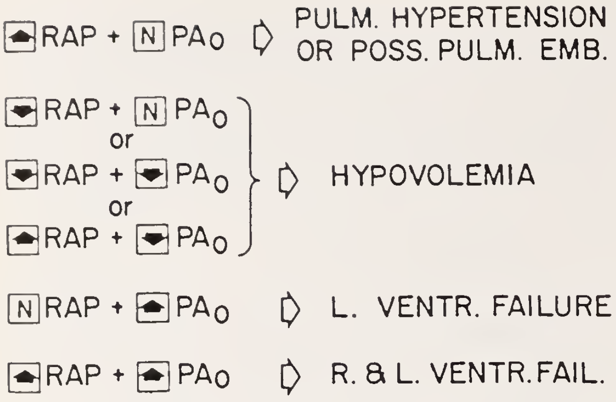

Fig. 3. Combinations of right atrial pressure (CVP) with pulmonary artery occlusive pressures and their interpretations.

red blood cells during hemodynamic resuscitation of the critically ill or injured patient. According to animal and clinical data (11) there is no deleterious cardiopulmonary effect when large quantities of balanced salt solution are given to normalize organ function during resuscitation.

Not every patient with low blood pressure in the recovery room gets the 250 ml of crystalloid solution as recovery treatment. We can summarize special situations which need a special type of treatment as post transurethral resection prostate, hyponatremia, hypokalemic arrhythmia, neurosurgery, anemia and angina, coagulopathy and cirrhosis. The use of vasoconstrictors in treatment of hypovolemic shock may return blood pressure to normal despite the presence of significant reduction in cardiac output and tissue flow. While in the recovery room we have the privilege of looking after many organs, the kidney gets special attention because it is difficult to reverse the damage should it happen.

If the kidney is treated at the expense of the lung, remember that there are several defense mechanisms before pulmonary edema. The alveolacapillary membrane is anatomically distinct from the area where interstitial edema accumulates. This is not happenstance but a reflection of the fact that collagen fibrils, which attract sodium and water, are located in the thick portion of the septum. A greater appreciation for lymphatic function (12) will be necessary since it can compensate for simpile increase in filtration, effect functional evacuation of the interstitial space to create the negative interstitial fluid pressure, and affect interstitial protein washout. Finally, the gell state preserves our physique. 99% of our interstitial fluid is contained in a gel state to enhance our body image. However, once interstitial pressure exceeds the capacity of the interstitial volume of compensate, interstitial fluid accumulates in the free state which ultimately results in gravitationally distributed edema: ankle edema when standing or paroxysmal nocturnal dyspnea when fluid translocate to the lung at night.

It is not that difficult to make informed decisions regarding the use of volume loading, inotropic and chronotropic drugs, vasodilators and beta adrenergic blocking agents in patients in the recovery room. All it requires is the ability to relate several classical physiologic concepts to clinical care.

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Perioperative Fluid Management

Louis R. M. Del Guercio, M.D.

Fluid management of high-risk surgical patients requires accurate preoperative assessment of cardiac, pulmonary and oxygen transport function. Optimum circulating volume under varying conditions of stress can only be determined in relation to the optimum function of these organ systems. The methodology which we have found useful in this regard is the automated physiologic profile that's analogous to the SMA-12 blood profiles; it collects measurements of 25 physiologic parameters most useful in evaluating the high-risk patient and graphs them out on a single page so a physician can tell at a glance the adequacy of venous return relative to the state of cardiorespiratory and metabolic function.

The big advantage of the graphic output, which is done with the help of a minicomputer, is that it makes the monitored parameters far easier to use. Once the values are determined they're plotted in bar-chart format on a sheet preprinted with normal ranges so you can see rapidly which ones are abnormal and by how much.

The information given by the profile includes the pressures in the heart and pulmonary artery measured through a right-heart catheter, as well as seven other hemodynamic values: cardiac index, pulse rate, stroke index, left ventricular stroke work, total peripheral resistance, right ventricular stroke work, and pulmonary vascular resistance.

Six other values included on the sheet relate to the adequacy of the patient's oxygen transport: arteriovenous oxygen difference, total oxygen consumption, venoarterial admixture, serum lactate, arterial base excess, and the value for the patient's blood of P_{50}, an indicator of oxygen affinity. P_{50} is defined as the oxygen tension at which the hemoglobin is 50% saturated with oxygen—at normal pH and temperature, a PO_2 of about 27 mm Hg—and indicates the position of the whole oxyhemoglobin dissocition curve. When the P_{50} is low, the curve is shifted to the left and indicates an increase in the blood's oxygen affinity, whose principal effect is to reduce the amount of oxygen the blood releases to the tissues. A high P_{50} means the curve is shifted to the right and the oxygen affinity is decreased. And there's a ventricular function graph that gives you an idea of the adequacy of the patient's cardiac reserve.

One of the most obvious applications of such a study preoperatively would be in myocardial failure. Hemodynamic and oxygen transport indicators will indicate pump failure before it becomes clinically apparent, when there's a better chance that you can do something about it. There are times when monitoring is useful in the diagnosis of perioperative myocardial infarction, too, for in an acutely ill patient who's going into shock it can be difficult to distinguish myocardial infarction from a pulmonary embolism when the electrocardiogram does not show immediate changes. Both pulmonary embolism and myocardial infarction are low cardiac output states. The difference is that in pulmonary embolism you find markedly elevated pressures in the right side of the heart, particularly the right ventricular end-diastolic pressure. In the early stages the wedge pressure is not elevated as it would be in MI but you may even have trouble floating the catheter into the pulmonary artery because of reduced pulmonary blood flow.

Fluid management on a physiologic basis is critical when the heart turns out to be a target organ in many other forms of shock. A myocardial depressant factor of some sort is known to exist in the severely burned patient, for example, and the profile can very often demonstrate an occult myocardial failure that responds to therapy. And it's been shown that after hemorrhagic and traumatic shock there are factors that affect previously normal cardiac function.

The profile takes a lot of the guesswork out of

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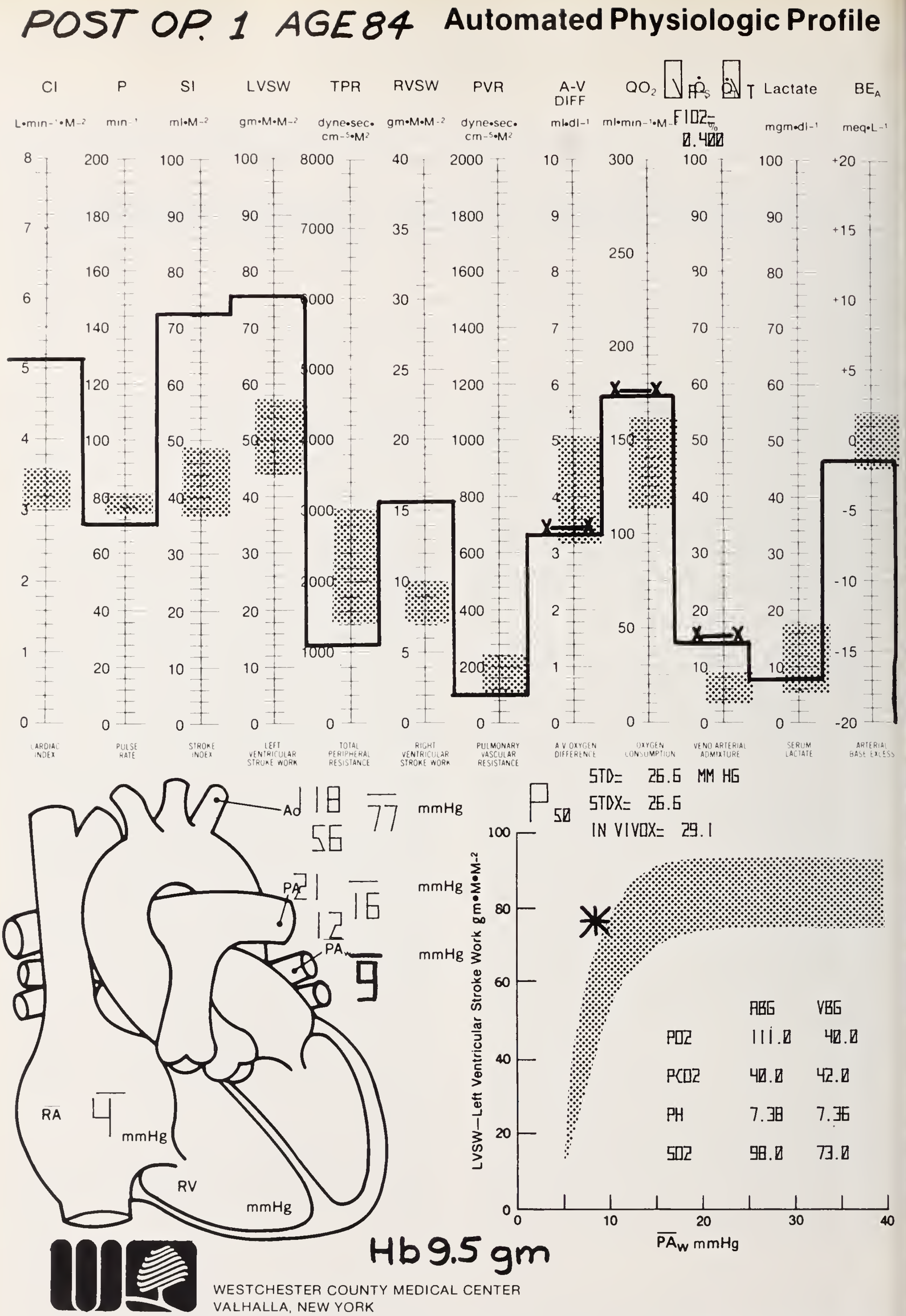

FIG. 1. Automated physiologic profile on the first postoperative day in an 84-year-old woman who had undergone a cholecystectomy with a cholecystoduodenal fistula. Adequate preoperative assessment and physiologic "fine tuning" assured a good postoperative profile demonstrating the increased circulatory and metabolic requirements in response to the stress of anesthesia and surgery. Note the good ventricular performance, increased oxygen consumption and moderate elevation of pulmonary shunting. The normal serum lactate indicates that oxygen requirements are being met.

evaluating cardiovascular status of all critical patients. A patient may be maintaining his blood pressure but with the hemodynamic variables charted side by side you can tell at a glance just how he's maintaining it. In many cases of profound shock, the blood pressure you observe is normal or nearly so because of peripheral vasoconstriction. When a drop in blood pressure finally does occur, it may be precipitous and too late for supportive measures to be of much help.

The only generally acceptable definition of shock during anesthesia and surgery, is an acute situation in which less oxygen is being delivered by the blood than is needed by the tissues. And the only way you can see that happening with certainty is that lactate, the end product of anaerobic metabolism, builds up in the blood. So an elevated blood lactic acid on the profile is a key feature in recognizing these poor perfusion syndromes during surgery.

To tell why oxygen delivery is inadequate, you need the various oxygen transport indicators provided by the profile. Shock has traditionally been classified as either anoxic, anemic or stagnant. In anoxic shock, as occurs with pneumonia or pneumothorax, that blood is never oxygenated in the lungs. In anemic shock that blood just isn't capable of carrying enough oxygen, for instance in carbon monoxide poisoning. Stagnant shock, of course, means that the blood isn't being moved to the tissues fast enough, as in any type of myocardial failure.

To these you should add two classes that have been defined more recently: histotoxic and affinitive hypoxia. Histotoxic hypoxia is a state in which the tissues are incapable of taking up the oxygen the blood delivers, while in affinitive shock the blood is oxygenated normally in the lungs but holds the oxygen so tightly it doesn't release enough in the tissues. Thus, even when cardiac output and arterial blood gases seem to be perfect, shifts in the oxyhemoglobin dissociation curve, arteriovenous shunting, or histotoxic factors reflected in the profile can bring about fatal cellular oxygen deprivation before you would suspect what is wrong with the patient's clinical appearance.

Surgery in patients who are septic is particularly hazardous. Although it can appear with low flows and myocardial suppression, in which case inotropic agents would be indicated, some patients can have elevated cardiac output or a hyperdynamic shock syndrome that's readily identified on a physiologic profile chart. The total oxygen consumption may be elevated along with the cardiac index and the pulse, while the total peripheral resistance drops. But the serum lactate level also rises, meaning that the patient is being forced into anaerobic metabolism.

To keep tabs on a critically ill patient's blood, the profile's side-by-side display of serum lactate and blood buffer base excess is particularly useful. The base excess, is a measure of the fixed acids and bases in the blood, so it shows you the degree of metabolic alkalosis or acidosis exclusive of changes due to CO_2 concentration, since the pH effect of CO_2 is easy to evaluate from the blood gases. The base excess or deficit would show you diabetic acidosis, acidosis caused by renal failure, or lactic acidosis resulting from anaerobic metabolism.

In hypoxic acidosis, you would see a rise in the lactic acid level and a decrease in the blood buffer base excess. The reason we display both of them is that many doctors react to hypoxic acidosis by flooding the patient with bicarbonate, which gives the patient a big sodium load that puts a strain on the heart and, although this may correct the base deficit, it reduces the oxygen delivery by shifting the oxyhemoglobin dissociation curve back to the left. It just masks the hypoxic acidosis and the direct lactate reading will show you that. So, by displaying both the lactate and the base excess, we keep things in better perspective.

Two more indicators that can reveal what's going wrong in a patient who's sinking into shock are the arteriovenous oxygen difference and the venoarterial admixture. When shock is caused by inadequate delivery of blood to the tissues, you'll see rising lactate, of course, and you may see good arterial blood gases and an acceptable P_{50} and hematocrit. But as the oxygenated blood sluggishly passes through the increasingly hypoxic tissues, a greater-than-normal percentage of its oxygen will be extracted and the arteriovenous oxygen difference, which is just the difference in oxygen saturation of venous and arterial blood, will rise. In increasing AV oxygen difference, this is a sign of shock due to low cardiac output.

The venoarterial admixture, on the other hand, is an indicator of pulmonary trouble. It's essentially a measure of shunting in the lungs or the percentage of the pulmonary blood flow that passes through unoxygenated alveoli. Venoarterial admixture is a sensitive measure of almost any type of pulmonary problem that may be developing acutely but it's particularly important as a very early sign of developing shock lung, the respiratory distress syndrome. It will show that long before there are any roentgenographic changes.

One of the most sensitive physiologic indicators in the profile is a singlepoint, left ventricular function plot that lets you evaluate at a glance not just the volume of blood the heart's putting out but the efficiency of its function. The profile program figures out the volume of blood contained in the heart and lungs by analyzing the dilution of a bolus of indocyanine green dye that's injected through the Swan-Ganz catheter. Volume replacement during surgery can best be titrated on the basis of changes in the ventricular function curve. Frequently, concomitant inotropic therapy or after load reduction are required for optimum function. Such "fine tuning" is the cornerstone of modern perioperative fluid management.

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ERRATUM

In Vol. 48, #3, May–June 1981, pp. 202–203: Figures 1a and 3a were inadvertently reversed in Dr. Eliasoph's article entitled "Metastasis Versus Pancreatitis Affecting the Transverse Colon."

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Renal Failure

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Alterations in renal function often become a management problem in the immediate postoperative period. An abrupt decline in renal function, an event which we define as acute renal failure (ARF), is the change usually noted. The decrease in kidney function may occur in an individual without an underlying renal disorder or may be superimposed upon a pre-existing disease. The anesthesiologist is frequently the primary physician involved in both diagnosis and management when a change in renal function occurs during surgery or in the immediate postoperative period. In addition, the anesthesiologist should be aware of circumstances in the preoperative period that may alter function during or immediately after a surgical procedure.

In this brief survey, acute renal failure will be described as currently encountered in the surgical setting, with particular emphasis on factors leading to its development. The diagnosis and management of acute renal failure in the immediate postoperative period will also be discussed.

Classification

The causes of acute renal failure, as generally found in the surgical setting are divided into five categories (Table I). This classification is quite arbitrary since the etiology and pathophysiology of acute renal failure in many, if not all, cases are multifactional. Nevertheless, the classification has been chosen to highlight conditions or circumstances that anesthesiologists should consider in a patient with an abrupt decline in renal function.

I. Intrinsic Renal Disease

It may seem unlikely that intrinsic kidney disorders such as glomerulo-nephritis, vasculitis, urate nephropathy, or myeloma would be the concern of the anesthesiologist. However, an awareness that an abrupt decrease in renal function may be due to intrinsic disease of the kidney, suspected but not confirmed preoperatively, will better prepare the anesthesiologist to consider alterations in a number of therapeutic maneuvers—for example, recognizing that potassium-containing solutions should be given judiciously, that fluid administered during surgery may have to be restricted, that doses of anesthetic and of other drugs given intra-operatively may have to be altered.

II. Disorders Decreasing Renal Blood Flow

The anesthesiologist is often called upon to manage circumstances leading to renal hypoperfusion, either during or following surgery.

Hypovolemia is an important cause for decreased renal flow. Reduced blood volume may be caused by hemorrhage, burns, fluid loss from the gastrointestinal tract, from preoperative or intra-operative use of diuretics, and from sequestration of fluids in various body compartments. In addition, cardiovascular events, such as myocardial infarction, arrhythmias, cardiac tamponade or vascular occlusive disease, may lead to decrease in renal blood flow and subsequent development of acute renal failure. Renal hypoperfusion due to volume depletion, cardiac failure and peripheral vasodilitation is generally diagnosed with relative ease, especially when the patient is carefully monitored with the sophisticated techniques now available for use during surgery, in the recovery room, and in the intensive care unit. Nevertheless, prolonged renal hypoperfusion remains the most common cause of acute renal failure occurring in the intra-operative period (1).

III. Toxins

Acute renal failure may occur under circumstances such as mismatched blood transfusions with subsequent intravascular hemolysis and

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TABLE I
Classification of Acute Renal Failure

I. **Intrinsic Renal Disease**
   glomerulonephritis, vasculitis, malignant hypertension, papillary necrosis, urate nephropathy, myeloma

II. **Disorders Decreasing Renal Blood Flow**
   Hypovolemia: hemorrhage, gastrointestinal losses, diuretics, sequestration of fluids
   Cardiovascular: myocardial infarction, arrhythmia, cardiac tamponade, vascular occlusion

III. **Nephrotoxins**
   Pigments: hemoglobin (transfusion reactions, intravascular hemolysis)
      myoglobin (muscle trauma and disease, coma, seizures, exercise)
   Antibiotics
   Anesthetics
   X-ray contrast media
   Prostaglandin synthesis inhibitors

IV. **Sepsis**
V. **Obstruction**
   Postrenal: stones, neoplasm, prostate, surgically induced, ruptured bladder
   Intrarenal: uric acid, hypercalcemia

from muscle injury or disease with the intravascular release of myoglobin. In recent years, transfusion reactions are less common due primarily to improved blood analysis techniques (2). Rhabdomyolysis, with resulting myoglobinuric acute renal failure, remains a reasonably frequent cause of acute renal failure. My personal experience stems from the care of a number of neurosurgical patients undergoing prolonged surgical procedures, during which they were positioned in a modified knee-chest position. During surgery, the anesthesiologist's records revealed that vital signs, oxygenation and cardiac function were stable and well-maintained. No reduction of urine output was noted throughout the intraoperative period. In the immediate postoperative period, however, there was an abrupt decrease in urine volume without any significant change in blood pressure, pulse, cardiac or pulmonary function. On physical examination, there was a marked increase in the circumference of the thighs. Laboratory studies showed that the scanty, dark-appearing urine contained myoglobin and that plasma levels of muscle enzymes were elevated. These patients had rhabdomyolysis secondary to prolonged pressure to the thigh muscles. The intravascular release of the myoglobin, in association with volume depletion, led to the development of acute renal failure.

Diagnostic agents and drugs used in the preoperative period may have nephrotoxic potential. In the 1950's and 60's, nephrotoxins of this type were identified as the cause of acute renal failure in approximately 8% to 10% (3, 4). Recently, the incidence of acute renal failure as a consequence of drugs, anesthetic agents, or contrast media has been reported to range from 30% to 35% of cases (5).

It is now appreciated that many antibiotics have a considerable nephrotoxic potential. The aminoglycoside antibiotics, such as gentamicin and tobramycin, commonly produce renal dysfunction (6, 7). Other antibiotics, including the cephalosporins, penicillin and the penicillin homologues are also potentially nephrotoxic (8–11). There may be difficulty in diagnosing antibiotic induced nephrotoxicity since the renal insufficiency is gradual in onset and often nonoliguric (urine output greater than 20ml/hr.) (10, 12).

When renal failure follows an operative procedure, it is important to consider anesthetics as a possible contributing cause for renal dysfunction. Methoxyflurane is the anesthetic most frequently implicated (13). The renal toxicity of methoxyflurane appears to relate to the level of plasma fluoride concentration (13). When there has been hepatic microsomal enzyme induction, such as follows barbituate administration, more rapid drug metabolism, with a higher concentration of the plasma fluoride may result. Enflurane, another fluoride containing anesthetic, apparently releases less fluoride than methoxyflurane, explaining its lower renal toxicity (14). Renal hemodynamic changes during general anesthesia have been well-documented for other commonly used anesthetics, including cyclopropane and halothane and may well be contributory to renal dysfunction in the post-operative period (15, 16).

It has now become increasingly evident that infusion of radioopaque contrast media may cause acute renal failure or lead to a worsening of renal function (17). It is not uncommon in a preoperative evaluation that an intravenous pyelogram, angiogram, CT scan or other diagnostic studies be performed. When a large amount of contrast material is administered immediately prior to surgery, acute renal failure may not be diagnosed until the postoperative period. Patients most likely to develop acute renal failure following the radiocontrast media generally are those 1) greater than 55 years of age, 2) with diabetes mellitus for more than ten years, with vascular complications, 3) with proteinuria, 4) who are dehydrated, 5) who have recently received other potential nephrotoxic drugs, and 6) in whom there is pre-existing renal insufficiency (17–19).

Another group of potentially nephrotoxic agents include indomethicin, phenylbutazane, naproxen, or other agents used for the treatment of a variety of arthritic conditions. These drugs are inhibitors of prostoglandin synthesis (20). It has now become increasingly apparent that the renal prostaglandins are important intrarenal vasodilators (21–23). Inhibition of renal prostaglandin synthesis results in local intrarenal vasoconstriction and more severe renal ischemia whenever a hemodynamic insult occurs.

IV. Sepsis

Infection is listed in a separate category because it remains one of the most common causes of acute renal failure and, in addition, is the most frequent complication following the development of the acute renal failure (2). In a recent survey, it was found that greater than 50% of patients developing acute renal failure postoperatively followed elective surgery. Gastrointestinal operations, and cholecystectomies were the procedures most frequently performed (2). In these cases, infection was the most frequent cause leading to the development of acute renal failure. Peritonitis was a common finding, whether related to the underlying disease process or suture dishisence. Other disorders associated with acute renal failure and a high incidence of fatality included pancreatitis, extensive burns and diffuse pulmonary infection.

V. Obstruction

Obstruction of urine flow anywhere along the genitourinary tract may cause acute renal failure. Early recognition is important since it is usually reversible. Obstruction in the immediate postoperative period is more easily detected these days with the availability of such noninvasive techniques as bedside x-rays, renal ultrasound, and renal scan. It is important to remember that the acute cessation of urine flow in the patient with an indwelling catheter demands that the patency of the catheter be ascertained.

Diagnosis

In the immediate postoperative period, the cause for an alteration in renal function is often readily apparent. Blood loss, volume depletion or marked vasodilatation are usually accompanied by changes in cardiovascular hemodynamics. Obstructive uropathy generally may be excluded with relative certainty. A careful review of the preoperative history and management will frequently uncover evidence of intrinsic renal disorders or potential nephrotoxic agents. In a considerable number of cases, however, it may be difficult to ascertain whether a decrease in kidney function is due to renal hypoperfusion that, if reversed, can lead to a restoration of renal function. Analysis of the biochemical composition of the urine often helps in establishing the diagnosis.

When there is renal hypoperfusion, urine osmolality is usually greater than 500 mOsm/KgH$_2$O, urinary sodium less than 20 mEq/1, plasma to urea nitrogen ratio greater than eight and the urinary to plasma creatinine ratio greater than 40. In contrast, patients in whom there is either nonoliguric or oliguric acute renal failure, the urinary osmololity is usually less than 350 mOsm/Kg H$_2$O, urinary sodium concentration greater than 40 mEq/L, urine to plasma urea nitrogen ratio less than three and the urine to plasma creatinine less than 20. These urinary measurements will generally discriminate approximately 80% of patients with a falling urinary output into one of these two categories (24).

Management

On occasion, the urinary indices indicate that oliguria is consequent to hypoperfusion without any apparent underlying detectable cause. It has been suggested that progression of the renal dysfunction to overt acute renal failure with structural changes can be prevented by maneuvers that increase solute excretion (25, 26). Isotonic or hypertonic mannitol solutions or a potent diuretic with proper replacement of urinary fluid losses are usually administerd (25).

There is some evidence to suggest that, even in cases in which the renal impairment has progressed to overt oliguric renal failure, there may be benefit in converting oliguric acute renal failure to a nonoliguric state (12). Recent studies have reported that there is a lower mortality in nonoliguric acute renal failure (26%) compared to oliguric acute renal failure (50%). In addition, morbidity is lower in the patients with nonoliguric acute renal failure. Thus there is less likelihood for development of infection, gastrointestinal bleeding, and fluid overload. Finally, only 28% of patients with nonoliguric acute renal failure require dialysis compared to 84% with oliguric acute renal failure. These advantages are present when the nonoliguric acute renal failure was spontaneous or followed its conversion from an oliguric acute renal failure by the administration of a diuretic or a solute load.

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The Recognition of Acute Myocardial Infarction Occurring During the Immediate Postoperative Period

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The incidence of ischemic heart disease has almost reached a state of pandemic proportion. According to data compiled by the American Medical Association in 1977, 29 million Americans are afflicted with some sort of cardiac or circulatory disease (1). In 1979, cardiovascular disease accounted for almost one million fatalities in the United States alone, representing more than half of all reported deaths (2). Many patients present with acute myocardial infarction or sudden death as the first clinical manifestation of cardiovascular disease. In addition, elderly and diabetic patients may have asymptomatic myocardial ischemia that passes unrecognized by both patient and physician. These facts indicate that we as anesthesiologists may be faced with increasing numbers of patients with cardiac disease. The immediate postoperative period, during which the patient is transferred to the recovery room, represents a particularly hazardous time for this group of patients.

Patients with previous manifestations of ischemic heart disease such as myocardial infarction, angina pectoris, and heart failure should be labelled "high risk." The physician should also be aware of potential problem patients such as elderly hypertensive patients with multiple risk factors (3). Recovery room personnel should be informed of medical history, status of the patient, preoperative medications, anesthetic management and hemodynamic function during surgery. Special attention should be focused on fluid balance.

In a study of preoperative factors related to the development of postoperative life-threatening or fatal complications, Goldman (4) found an increased risk in patients with resting EKG abnormalities. Frequent premature contractions are also important because they may indicate severe heart disease and may be associated with other ventricular dysrhythmias.

In patients with a previous myocardial infarction, the overall incidence of reinfarction is high. Tarhan (5) and Steen (6) at the Mayo Clinic found that if infarction had occurred within the three months prior to surgery, the rate of reinfarction was 27%–37%. Three to six months preoperatively, the incidence of reinfarction was 10%–16%. Six months postinfarction, the risk of infarction associated with surgery falls to 5%–7%. Patients with no clinical evidence of ischemic heart disease have a low incidence of myocardial infarction during anesthesia and the postoperative period.

The literature on this subject is conflicting. Since many of the patients who died did not have an autopsy, the clinical diagnosis was not always confirmed. McClure (7) reported one death in 3,400 operations, but the age factor was not considered. A study in the same age group of patients with reinfarction or a new infarct is not available. A previous "silent" myocardial infarct will obviously be of great statistical importance in any future study.

The most important challenge for the recovery room staff is the recognition of acute myocardial infarction in the group of so-called "healthy patients." An important consideration is the early recognition of failure in an organ subsystem. Time is of the essence. Prompt diagnosis and immediate treatment are vital if these patients are to be salvaged. To recognize an acute myocardial infarction during the immediate postoperative period and to make a differential diagnosis from other causes that may resemble this condition, we must utilize the following parameters in the recovery room:

1. hemodynamic monitoring

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2. EKG
3. enzyme determinations
4. cardiac radionuclide scanning (if necessary).

The recognition of ischemic episodes during the immediate postoperative period and the differentiation of left and right sided heart failure requires an understanding of myocardial oxygen balance. This is the balance between the myocardial oxygen supply and myocardial oxygen demand and it must be preserved at all times. Maximal effort should be made to maintain myocardial oxygen supply without increasing demand. In addition to maintaining myocardial oxygen supply by preventing hypoxia, a reduction in coronary blood flow resulting from period of hypotension must be avoided. Cardiac brady and tachydysrhythmias may also cause hypotension and interference with coronary perfusion. Additional factors that stress the heart by increasing metabolic demand and hence oxygen consumption include pyrexia, hyperthyroidism, and other causes of tachycardia such as beta adrenergic agonists.

Another deleterious factor that predisposes to ischemia is increased myocardial wall tension. This can occur either as a result of increased preload (diastolic filling pressure) or increased afterload (represented by increased peripheral resistance). An increased preload is most commonly due to fluid or volume overload, while an increased afterload may be caused by alpha-adrenergic drugs such as metaraminol and phenylephrine. In addition to maintaining myocardial oxygen supply, any reduction in blood flow must be avoided. Such a reduction may result from hypotension, tachycardia, increased left ventricular filling pressure, increased coronary resistance, and hypercoagulation.

The main factors that increase myocardial oxygen demand include increased contractility, increased wall tension, increased preload, increased afterload, tachycardia, and major dysrhythmias.

Indirect information concerning coronary perfusion pressure is important. This is equal to the diastolic blood pressure minus the left ventricular filling pressure.

These factors must all be taken into account and controlled during the immediate postoperative period. It is important to realize that they may result in a vicious cycle of ischemia precipitated in the recovery room, as described by Kaplan (8).

Myocardial ischemia can produce myocardial dysfunction and an elevated left ventricular pressure, compromising the coronary circulation and producing ischemia and left ventricular dysfunction. In addition, ischemia may result in dysrhythmias which can impair myocardial function. Tachycardia and increases in preload are the most poorly tolerated factors, since they not only decrease the oxygen supply, but also increase the myocardial oxygen demand.

The result of prolonged myocardial ischemia is myocardial dysfunction and ultimately myocardial cell death and infarction. Severe myocardial dysfunction can result in decreased cardiac output with decreased systemic perfusion, hypotension, and an increase in pulmonary capillary wedge pressure.

The following is an illustrative case history: A 45-year-old bank executive with no previous medical problems, except for two episodes of cholecystitis, was admitted to the hospital with a diagnosis of cholelithiasis. He was scheduled for an elective cholecystectomy. His preoperative laboratory test results and EKG were normal. His blood pressure was slightly elevated. The anesthetic and operative courses were uneventful. The patient was extubated in the operating room at the end of the case. On admission to the recovery room, the patient responded to verbal commands and vital signs were normal. Thirty minutes after admission to the recovery room the patient complained of a short period of discomfort and pain in the lower chest and upper abdomen near the upper part of his incision. In retrospect, the patients' presurgical history included similar episodes of presumed "cholecystitis" which may in fact have been angina pectoris. He was diaphoretic, peripherally cyanotic, agitated and becoming more confused. Vital signs revealed a significant decrease in systemic blood pressure and a sinus tachycardia.

Pulmonary wedge pressure was 25 torr and cardiac output and index were low. Our diagnosis was cardiogenic shock. An electrocardiogram confirmed the diagnosis of acute myocardial infarction by demonstrating Q waves, S-T segment elevations, and T wave inversions in leads V_1 to V_5 corresponding to the anteroseptal portions of the myocardium.

In addition to clinical evaluation of the blood pressure and pulse, basic noninvasive hemodynamic evaluation of the patient in the recovery room involves recordings of blood pressure, temperature, an electrocardiogram, and a chest x-ray. Level of consciousness, urine output, skin color and temperature must also be monitored.

A well organized and suitably equipped recovery room should be capable of prompt analysis of hemodynamic deterioration, in order to establish the diagnosis and best direct treatment. Invasive monitoring is essential in every complicated case. The arterial line offers continuous monitoring of blood pressure and facilitates blood gas sampling. The flow directed pulmonary artery catheter—the Swan-Ganz catheter—allows monitoring of the right atrial, right ventricular, and pulmonary capillary wedge pressure which is an accurate reflection of left ventricular end diastolic pressure. Cardiac output by the thermodilution technique may also be measured using the Swan-Ganz catheter.

The data obtained are useful for the differentiation between hemorrhagic shock, cardiogenic shock and pulmonary embolization. They aid in the choice of vasoactive agent or fluid replacement; they may even indicate reoperation for surgical bleeding.

The insertion of an intra-arterial line and a Swan-Ganz catheter is now considered routine in complicated cases and has become an established technique in community hospitals as well as in large medical centers.

The detection of EKG changes during myocardial ischemia is an important diagnostic clue, but may be falsely negative or equivocal in up to one third of patients. In addition, patients with conduction abnormalities or pacemakers may not manifest their ischemia on the surface electrocardiogram. Most useful are changes in the S-T segment, particularly in leads V_5 and V_6. Acute S-T elevation is usually a sign of transmural ischemia or infarction, while S-T depression represents subendocardial ischemia or infarction. The development of new Q waves usually confirms the diagnosis of myocardial necrosis although, occasionally, it may be transient and represent reversible ischemia. T wave inversion, although frequently a sign of subendocardial injury, is the least specific of the EKG changes. Other factors such as pH and electrolyte disturbance, may mimic myocardial ischemia by causing similar EKG changes. This is true not only of S-T segments and T waves, but even transient conduction abnormalities and Q waves may occur with hyperkalemia and acidosis.

Other diagnostic examinations such as the routine chest x-ray may show atelectasis, pulmonary vascular congestion or changes in heart size when compared with preoperative films. Unfortunately, for technical reasons, bedside chest x-rays are frequently difficult to compare with preoperative baseline films.

Although usually not helpful in the acute diagnosis and management phase (first few hours), serial enzyme determinations are useful and sensitive tests for myocardial infarction. The CPK-MB isoenzyme is a specific and highly sensitive indicator of myocardial necrosis. The increase in enzyme activity occurs approximately six to eight hours after infarction with a peak at 24 hours.

Cardiac radionuclide imaging using a bedside gamma camera is currently a useful and reliable method for diagnosing acute myocardial infarction within the first 24 hours. Several methods of nuclear imaging are in use:

1. Technetium-99 pyrophosphate scintigram for acute infarction (9, 10)

The scan becomes positive in six to twelve hours, but the ideal time is 24–48 hours postinfarction. This test is equal to the CPK-MB, with a sensitivity of more than 95% for the diagnosis of transmural infarction and 75% for subendocardial infarction. This method has several drawbacks, mostly false positive readings due to soft tissue necrosis, pericarditis, or calcified tissue within the heart.

2. Thallium 201 perfusion scintigrams (11, 12)

A monovolent cation, similar to K^+, thallium moves intracellularly, therefore, viable myocardial cells take up thallium. If there is a myocardial infarction, no thallium will be taken up in the infarcted area. Thus, thallium perfusion scintigraphy will be positive immediately after an acute myocardial infarction. A thallium study is better than an EKG for localizing the area and size of myocardial injury, also in subendocardial infarcts this method is useful in approximately two thirds of patients. If the thallium defect is transient (present only during an episode of chest pain) then the myocardium is still viable and the ischemia was transient. If the defect is permanent after an episode of chest pain, this is reliable diagnostic documentation of an acute myocardial infarction. In general, the size of the thallium perfusion defect correlates well with the anatomic lesion.

3. Gated blood pool scintigraphy—the most useful test (13, 14)

Technetium-99 labeled albumin or red blood cells are injected intravenously and images are recorded by a gamma camera and microprocessor. This allows separation of the cardiac cycle into diastolic and systolic images and a cine of the moving heart can be generated in a few minutes.

Using the microprocessor, several very important parameters of cardiac function can be accurately measured, including left and right ventricular ejection fractions and regional wall motion.

By using gated blood pool scintigraphy, regional wall motion abnormalities resulting from ischemia or infarction can be visualized. Left ventricular dysfunction is the earliest sign of ischemia or dysfunction and may precede chest pain and EKG findings. This method allows for accurate noninvasive bedside assessment of acute myocardial infarction, evaluation of both left and right ventricular function, quantification of mitral or aortic regurgitation and diagnosis of ventricular aneurysm. Although the resolution of this technique is not sufficient to visualize coronary arteries, the method has been validated against the "gold standard" of contrast angiography for analysis of ventricular function.

In conclusion, the early diagnosis of acute myocardial ischemia and infarction during the immediate postoperative period is a very difficult but necessary challenge. Highly competent staff in the recovery room, using all available diagnostic methods (hemodynamic, EKG, laboratory and scanning) may well save many victims of acute myocardial infarction. In addition, coronary angiography and emergency coronary artery bypass graft operations can be successfully performed in many patients after the ischemic myocardium is stabilized with medications or intra-aortic balloon pumping.

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The Use and Abuse of Diuretics

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The use and abuse of diuretics is a neglected subject for discussion, although the overall mortality rate of 60% for acute renal failure has remained unchanged over the past 15–20 years (1). Initially, this statement may seem incongruous, but a logical connection between diuresis and renal failure is always invoked in discussions concerning renal failure. In fact, Brown postulated that in patients with compromised renal function the early treatment with lasix might prevent development of the oliguric form of acute renal failure (2). Indeed, concern over renal failure and its disproportionate effect on patient mortality has led Cullen and others to state that "the major goal of intensive patient care is the preservation of renal function." Therefore, the question of diuretic use will become important in its own right. Unfortunately, it will be impossible to segregate diuretics from an overall consideration of fluid and electrolyte homeostasis.

Any discussion considering use of a drug will require adequate means for assessing the results of its administration. Monitoring the effect will require input from the four areas involved in standard data collection—quantitative, qualitative, primary and derived parameters. Specifically, urine quality will be equally as important as quantity. Simple tests which should be performed in any recovery room or associated stat lab include:

1) diabetic fractionals
2) specific gravity
3) urine electrolytes
4) urine and serum osmolarity

More sophisticated data collection will also include additional blood chemistries and the calculation of renal clearance data:

5) BUN
6) Creatinine
7) Fractional sodium excretion
8) Creatinine clearance

However, much of the additional information requires extra time, and significant delays may exist between sampling and calculation of derived parameters. This delay may be unacceptable and Brown states that "changes in flow and concentrating ability of the kidney may occur rapidly and will be detected only if free water clearance (C_{H_2O}) is frequently monitored" (3). Therefore, it would seem reasonable to utilize a monitor of urinary function which is readily measured giving some degree of diagnostic accuracy and follows from our understanding of renal physiology and the filtering role of the glomerulus.

Common anesthetic practice incorporates infusion of a quantity of dextrose in water prior to induction. An explanation for this water load is that metabolism continues despite physician orders to guarantee starvation, and an osmolar load will be presented to the kidneys in the order of 600–800 milli osmoles on the day of operation. This will require additional free water so that osmolar excretion can occur, and dextrose is the most common source of water in currently used fluids. The ability of the kidney to clear plasma of osmotic debris with conservation of water gives the basis for the derived indices of renal function:

1) osmolar clearance
2) free water clearance

Osmolar clearance is expressed in a common clearance form:

$$\text{Cosm} = \frac{\text{Uosm} \times \text{Uvol}}{\text{Posm}}$$

and free water clearance follows from this as:

$$C_{H_2O} = \text{Uvol} - \text{Cosm}$$

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These results should be calculated frequently in patients suspected of being at high risk, and collection periods should be short in an attempt to follow acute changes which may be masked if collection time is prolonged.

Quite obviously, renal function and intravascular volume maintenance are inseparable, and Virgilio extended this interdependence when he stated that "the primary goal of fluid resuscitation in shock and trauma is the protection of major organ function by the rapid and safe restoration of hemodynamic stability" (4).

Surgical losses—the much discussed physiologic third space—have been well recognized for years, and Sherrington and Copeman reported "that simply incising the linea alba sufficed to increase the specific gravity of the blood especially if at the same time the abdominal contents were in any way disturbed" (5). A more familiar circumstance is witnessed daily in the operating room when the surgeon removes a wet, gloved hand from the abdominal wound. The moisture on the glove is not being infused into the patient, rather it is an example of obligatory removal. Histologic confirmation of these losses is possible.

The anesthesiologist's interactions with diuretics may be either as administrator or, and perhaps more importantly, as an unwilling or unknowing participant in their effect. Common diuretics include:

1) Furosemide
2) Mannitol
3) Ethacrynic acid
4) Digitalis
5) Dextrose
6) Alcohol
7) Inotropic agents

This list is far from complete and ignores all common agents chronically administered to patients with long standing hypertension or congestive cardiac failure. An excellent review of traditional diuretic use was written a few years ago (6). The addition of alcohol and dextrose may be surprising, but these are possibilities which all anesthesiologists must consider. Both will act as osmotic agents (in addition to hormonal effects) and may lead to false security in patients who maintain a diuresis in spite of a contracted extra cellular volume (ECV), hence, the importance of a qualitative assessment of quantity. Not only are the agents themselves important, but their related side effects are of prime concern in anesthetic practice. Diuretic effects include:

1) hyponatremia
2) hypokalemia
3) metabolic alkalosis
4) relative depletion of extra cellular volume
5) diagnostic confusion

The preceeding discussion may appear to contra-indicate the use of diuretics. This would be an extreme position; but, it serves to underscore the importance of administration of any drug for a specific indication. Undeniable use for diuretic therapy will be associated with the following conditions:

1) Volume overload
2) Left ventricular failure
3) Acute renal failure
4) Raised intracranial pressure
5) Transfusion reactions
6) Rhabdomyolysis
7) Aortic surgery
8) Cardiac surgery
9) Renal surgery
10) Gall bladder surgery
11) Electrolyte imbalance
12) Diagnosis

Bastron highlights the fact that there is an "apparent higher incidence of ARF in jaundiced patients or patients having peripheral vascular or gastrointestinal procedures in nonteaching hospitals compared with university hospitals" (7). He continues by wondering whether or not "this may be related to the emphasis on preoperative hydration at university centers" (8). Although the uses are multiple, the theoretic considerations relating to renal benefit appear to follow the simplistic belief that some urine flow is better than none irrespective of the means of producing the flow. Before discussing this further, the situations in which diuretic administration constitutes a pharmacologic abuse must be stated. They are:

1) Undiagnosed low urine output
2) Unstable hemodynamic state
3) Unmonitored response

Therefore, if the etiology of acute renal failure can be considered as either a tubular event (that is, both tubular back leak and tubular obstruction have been proposed) or a renal vascular event, it still remains of overwhelming importance to insure an optimal renal blood flow in order to maintain adequate glomerular filtration pressures.

The disadvantage of volume loading uppermost in people's minds is that of overhydration with resultant pulmonary edema. However, Walters stated, in a discussion concerning acute tubular necrosis, that "the fear of overtransfusion probably operates to the detriment of the patient far more than to his benefit" (9). The types of fluid used during resuscitation and surgery have received much recent publicity, and the decision whether or not to use albumin is as much emotional as scientific. Postresuscitation and postoperative hypertension are problems common to the anesthesiologist and treatment with a diuretic is often successful. Ledgerwood shed some light on this when she reported that the "intravenous administration of normal human serum albumin during resuscitation may contribute to the hypertension by impairing appropriate saline diuresis" (10), a situation which will obviously respond to decreased renal salt absorption. More importantly, it has been suggested that added albumin use may be detrimental. Lucas reports that "the increased mortality associated with albumin administration may be related to the underlying (renal) insult" (11). Indeed, diuretic administration is commonly required with albumin use (12), and the role of crystalloid resuscitation in reducing dependence upon dialysis has been suggested (13).

Therefore, there is an undeniable controversy not only concerning the types of resuscitative fluid but also over the perioperative use of diuretics. Jarnberg suggests because mannitol does not impair GFR and has milder effects on renal function than furosemide (14) it "should be used as the diuretic of choice in treatment of postoperative (posttraumatic) oliguria in patients without known cardiovascular disease" (15). Shin notes that "when postoperative renal dysfunction is recognized early and therapy is directed toward attaining optimal blood volume, oliguria in acute renal failure may be avoided" (16). However, he cautions against indiscriminate use of diuretics prior to effective volume replacement which "may aggravate hypovolemia and lead to renal failure" (17). Adequate replacement is highlighted in different fashion by Rhodes who observes that "increasing duration of hypoperfusion in traumatized man is associated with large losses of extracellular and particularly interstitial volume" (18) which may in part be due to "skeletal muscle membrane depolarization followed by intracellular influx of salt and water" (19).

The correct use of any diuretic will involve adequate resuscitation and restoration of optimum hemodynamic status. Once this is accomplished, diuretic need may be reduced. If a diuretic is chosen, any of the commonly available agents can be safely used at this time if adequate monitoring is available. As our understanding of underlying physiology improves and the postoperative effects of increased sympathetic tone and increased renin-angiotension levels are determined, relatively nonspecific, mass actions of diuretics may be replaced by a group of sophisticated agents which will have specific inhibiting actions. In the meantime, adequate preload augmentation followed by diuretic therapy is a safe practice in most instances, and may be beneficial in reducing the incidence of acute renal failure in the perioperative period. No diuretic agents should be employed unless a diagnosis of the oliguria has been reached. It must be remembered that following many procedures, an initial apparent oliguria when stimulated with a diuretic will result in an uncontrolled diuresis in the early postoperative period. This in turn may precipitate cardiovascular compromise secondary to both rapid volume depletion and significant electrolyte imbalance. An intelligent decision concerning appropriate diuretic therapy can only be made 1) when the physiologic factors associated with oliguria have been studied, 2) when controlled investigations on blood and urine have been performed, and 3) if adequate monitoring of drug administration is available. If these conditions are not satisfied, possible disastrous consequences may result from actions usually considered benign.

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Cerebral Resuscitation

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Pathophysiology

Because of the socioeconomic tragedies associated with severe permanent brain damage after cardiac arrest and resuscitation, a brain resuscitation laboratory research program was started in Pittsburgh in 1970 (1). This has evolved into systematic studies in rats, dogs, monkeys and, ultimately, in patients. Appraisals of brain resuscitation measures must keep in mind the following distinctions: 1) differences between ischemic, hypoxemic, traumatic, and other types of injury, 2) focal vs global ischemia, 3) incomplete ischemia (shock) vs complete ischemia (cardiac arrest), 4) pretreatment (protection) vs postinsult therapy (resuscitation), 5) initial insult vs postreperfusion changes, 6) early postinsult functional changes that may be reversible vs permanent brain damage as outcome, and 7) postinsult changes initiated by the initial brain injury vs brain damage caused by extracerebral complications after the insult (2, 3).

Although total circulatory arrest deprives the brain of energy within five minutes, cerebral neurons seem to remain viable much longer (4). Reperfusion, however, with current standard life support, is usually accompanied by multifactorial, inhomogeneously distributed deleterious events in the brain, that can result in multifocal necroses (miliary microscopic infarcts). Therapeutic potentials for ameliorating these events are suggested by the following identified factors in this postresuscitation disease (5): multifocal impairment of reperfusion (from blood cell sludging, vasoparalysis followed by vasoconstriction, and tissue edema) accompanied by hypermetabolism, tissue acidosis and irreversible membrane damage, in part possibly due to free chemical radicals (6–8). Animal models ideally should give a clinically relevant reproducible insult, and provide control of extracerebral variables postischemia long enough for secondary changes to mature, thus giving the therapy being tested a chance to work. Also, outcome variables should reflect irreversible damage, for example, long-term neurologic deficit and histopathologic damage.

Since the 1920s, there have been attempts made to understand and ameliorate brain damage from stroke, head injury and neurosurgery. It was not until the 1970's, however, that the term "brain resuscitation" for global brain ischemia (cardiac arrest) was proposed (1–3) and that evidence was provided of the potential to ameliorate postischemic encephalopathy (9). Since the pathogenesis of postischemic-anoxic encephalopathy is multifactorial, treatment potentials after the insult must be multifaceted. Probably, neither barbiturate nor any other single drug will evolve as a panacea for sick neurons. Rather, progressively developing combinations of physiologic and pharmacologic measures should be systematically studied, by first evaluating individual treatment potentials in relatively inexpensive animal experiments, then demonstrating the effect of therapeutic combinations in long-term animal experiments and, finally, designing clinical treatment protocols for controlled evaluation in monkeys and patients. Such systematic studies have been initiated at the Resuscitation Research Center of the University of Pittsburgh.

Laboratory Results

The first confirmation of treatable postarrest changes came from a study of dogs with 12 minutes of ventricular fibrillation (9). A combination of reflow promoting measures (intracarotid hemodilution to 25% hematocrit by dextran 40, heparinization and moderate hypertension), employed immediately after restoration of spontaneous circulation, significantly ameliorated brain damage. In later monkey experiments,

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heparinization alone and intravenous hemodilution alone did not ameliorate brain damage. Severe intermittent hypertension alone and hypotension worsened brain damage (10). The combination of hemodilution with sustained moderate hypertension appears promising and deserves controlled study.

A global brain ischemia monkey model with high pressure neck tourniquet, although clinically less relevant than cardiac arrest models, allows accurate control of insult time (completeness of ischemia confirmed by radio tracers, EEG, ICP, and angiography) and leaves extracranial organ systems unimpaired (11, 12). Using this monkey model, Bleyaert et al in the mid-1970's studied thiopental loading (90 and 120 mg/kg IV) and found that this treatment, if given early postischemia, ameliorates brain damage seven days postischemia (12). Although this is the only published evidence of a brain damage ameliorating effect after global brain ischemia, there are other documented beneficial effects of barbiturates: (a) Pretreatment protected against brain damage after total circulatory arrest (13) [another group, however, could not duplicate these results (14)]; (b) Thiopental and pentobarbital in conventional anesthetic doses (and even more so in large loading doses) diminished infarct size when given before or after experimental focal ischemia (15–17); (c) Methohexital given during global hypoxic ischemia in rabbits ameliorated brain damage (18); and (d) Barbiturates exert beneficial short-term effects on cerebral metabolism, blood flow (19) and intracranial pressure (ICP) (20). There has been no evidence that barbiturates per se can augment brain damage, provided ventilation and arterial normotension are controlled.

Problems with experimental design and control of extracerebral variables have plagued all animal studies of global ischemia (21). Safar's (9) and Bleyaert's (12) studies, started a flurry of interest in brain resuscitation. Small series of animals used, and nonconcurrent controls, all caused by inadequate funding, created some controversy about these results, although they were statistically significant. Reperfusion pressure patterns and duration of immobilization and controlled ventilation, which varied in past experiments, have later been found to possibly influence outcome (21). Therefore, four treatments are now being compared in larger series of global brain ischemia monkey experiments, with concurrent controls. The above and other variables are rigidly controlled: 1) controls, spontaneous breathing, 2) immobilization 48 hours, 3) thiopental loading (potentially cardiotoxic), and 4) thiopental anesthesia (not cardiotoxic) (Gisvold and Safar, work in progress). Preliminary results suggest that the circulatory side effects of thiopental, even in monkeys with healthy hearts, are unpredictable and not entirely related to thiopental blood levels. They are worsened by the preceding brain ischemia. Optimal types, doses and timing of barbiturate administration remain to be determined. The exact mechanisms by which barbiturates might diminish brain damage are unknown. Several beneficial effects, however, have been documented: decreased cerebral metabolism (22), increased oxygen supply/demand relationship and a reverse steal effect of CBF distribution (19, 23, 24), decreased ICP (20), and possibly decreased postischemic brain amines (7). Membrane stabilization by free radical scavenging (8) may not be a significant factor (25).

The idea of "putting the injured brain to rest" by "therapeutic anesthesia" (1–3), using relaxants (21) or hypnotics (12–20) remains to be proven effective. Treatments that deserve controlled laboratory investigation after global brain ischemia are many. Those that appear promising include various drugs and measures that decrease cerebral metabolism, improve cerebral reperfusion and intracerebral CBF distribution, prevent hyperactivity (seizures), normalize brain pH, supply substrate and energy, and protect membranes. Most promising appear various reflow promoting measures and hypothermia. The ability of *hypothermia* induced before and during the insult a) to protect against brain damage and b) to ameliorate focal ischemia when given early after artery occlusion (26) has been documented. Unfortunately, no controlled animal studies have been performed yet to examine the ability of hypothermia to ameliorate brain damage when induced early after cardiac arrest.

Clinical Results

For use after cardiac arrest and CPR, general brain oriented life-support guidelines for the management of the comatose patient have been developed, based on experimental and clinical data (1–3, 10). These guidelines include immediate establishment and maintenance of arterial normotension, immobilization with softening doses of a relaxant and moderate controlled hyperventilation, normalization of arterial pH, arterial PO_2 above 100 torr, moderate hyperglycemia, moderately low hematocrit, normal serum osmolality, colloid osmotic pressure and other blood variables, hydration with 5%–10%

glucose in 0.25%–0.5% saline (no dextrose in water), and hyperalimentation. Intracranial mass lesion must be ruled out. Pharmacologic doses of a corticosteroid are optional and adjunctive. Also optional is the use of conventional doses of thiopental, pentobarbital, diazepam or phenytoin for the prevention or treatment of seizures, to minimize afferent stimuli, to stabilize the patient under controlled ventilation, and to perhaps reduce brain edema and ICP (20, 27–30). Large loading doses of barbiturate are under controlled clinical investigation, but are not ready for wide clinical use because of their cardiac toxicity (34). Short-term early postarrest induced hypothermia (33°C) may be justified in patients with healthy hearts who have nothing to lose and much to gain, but is not yet recommended for patients with sick hearts, because hypothermia may cause life-threatening dysrhythmias, myocardial depression and increased blood viscosity. Osmotherapy has been used but not yet evaluated for its beneficial effect after cardiac arrest. Osmotherapy, if used, should be low-dose short-term, guided by monitoring of at least serum osmolality, and ideally also by monitoring of ICP.

ICP monitoring was developed for the management of patients after head injury or neurosurgery (27, 28). Indications for ICP monitoring after cardiac arrest are not clear, since after moderate global ischemic insults, ICP usually is not significantly elevated. Since transient moderate elevations in ICP postcardiac arrest can occur, we encourage more frequent use of ICP monitoring in comatose patients after cardiac arrest in order to learn. If ICP is found elevated above the normal 15–20 torr, an orderly sequence of action is recommended: 1) further controlled hyperventilating, 2) ventricular CSF drainage, 3) thiopental or pentobarbital 2–5 mg/kg IV, repeated as needed, 4) a loop diuretic, 5) osmotic diuresis (mannitol), 6) hypothermia. While severe ICP rise is clearly detrimental, particularly when it progresses to brain herniation, moderate increases in ICP and their therapeutic correction have not been clearly correlated with outcome (29), not even in cases of head injury.

ICP-reducing and potentially neuron saving therapies should be evaluated for cases of *encephalitis.* So far not much information is available. End stage Reye's syndrome (a toxic metabolic inflammatory encephalopathy) could be dramatically reversed with large doses of barbiturate (30); whereas ICP reduction by conventional measures failed to increase survival (31).

For acute severe ischemic stroke, we have recommended a resuscitative approach, starting in the prehospital phase of emergency care. Experimental reduction in infarct size, improved neurologic outcome or increased survival after focal ischemia have been suggested for moderate hypertension, hemodilution, steroid, hypothermia, hyperventilation and barbiturate (even in noncardiotoxic doses). These facts warrant controlled clinical trials (2, 15–17, 29).

Because of the promising experimental results by Bleyaert et al (12) with large dose thiopental loading in monkeys after global brain ischemia, a patient trial protocol for this treatment after cardiac arrest has been developed and peer reviewed in the mid-1970s (1). The protocol includes thiopental 30 mg/kg. Uncontrolled feasibility trials in 100 patients (32, 33) proved that this treatment is possible, that it is well tolerated by patients with healthy hearts, and that it can rearrest the sick heart, particularly when arterial pressure is not continuously controlled. Also, surprise recoveries after 10–22 minutes of total arrest made this treatment appear promising (32, 33). Since these feasibility trials were without control cases, proof or disproof of the efficacy of thiopental loading will come from a controlled prospective randomized trial which is now in progress in 12 institutions of eight countries coordinated by the Resuscitation Research Center of Pittsburgh (34). The initiation of this study raised many questions, including risk/benefit analysis, criteria for the selection of cases with poor prognosis, feasible timing of therapy, and the obstacles introduced by consent requirements. Results are to be expected by 1983.

Conclusions

To make cerebral resuscitation a positive force in public health, it should be combined with critical care triage (34). While during emergency resuscitation the outcome of the brain cannot be predicted, all efforts should be discontinued in cases of certified brain death several days after the insult; and extraordinary measures should be withdrawn after more than two weeks of irreversible vegetative state without brain death, to let the patient die (35). Research is needed to develop 100% reliable prognosticating criteria for patients with coma or vegetative state after cerebral insults. A systematic search for neuron saving measures after global brain ischemia and other cerebral insults is worthwhile and appears promising. Most likely, no single drug but rather a combination of pharmacologic and physiologic measures will evolve as the effective clinically feasible therapy, since the pathogenesis of postischemic anoxic encephalopathy is multifactorial.

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Duodenal Ulcer: An Update

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The topic of duodenal ulceration is one of the most rapidly changing in the field of gastroenterology, because our attitudes about the possible etiologic bases of the disease are in a state of extraordinary flux, while our ability to treat the disease has improved so dramatically that most of our current "knowledge" is out of date, if not positively misleading. This report represents a summary of a talk presented to the Department of Surgery in November 1980, at The Mount Sinai Hospital, New York.

The basic concept of our current views about the etiology of the duodenal ulcer is that gastric juice is somehow "aggressive" towards the duodenal mucosa and, in some individuals, is responsible for the genesis and persistence of the duodenal mucosal ulceration. This view of the etiology of the duodenal ulcer is the consequence mainly of the ease with which gastric juice can be obtained from patients, compared with the difficulties encountered when attempts are made to measure other alimentary functions.

The concept of "aggressive" gastric juice is based on three main principles. Gastric juice is always present in the stomach of patients with duodenal ulcer (summarized by the adage "No acid-no ulcer"). A number of observed pathophysiologic disturbances involving gastric secretion of acid or the fate of the secreted acid have been observed in association with duodenal ulcer. Medical and surgical therapy, designed to reduce gastric secretion, is followed by apparently more rapid, or more lasting, healing of duodenal ulcers than expected in untreated patients. How true are these concepts?

It is true that nearly all patients with a duodenal ulcer secrete acid (except a very few with apparent achlorhydria after gastric operations). However, it is also true that nearly all human beings secrete acid and that the amounts of acid secreted by ulcerated and nonulcerated individuals are virtually identical. It seems that a small proportion (less than 20%) of patients with a duodenal ulcer secrete more than nonulcerated individuals, but the majority secrete normal amounts of gastric juice.

The pathophysiologic disturbances detected in patients with a duodenal ulcer are considered to be so intimately linked with the etiology of duodenal ulcer that "pathophysiology" and "etiology" are used interchangeably. There is, of course, no necessary reason for inferring such linkage, since pathophysiologic alterations in function may be secondary to the ulceration or may represent coincident manifestations of some underlying disorder. In any case, and equally important, the current information about pathophysiologic abnormalities in duodenal ulceration is so contradictory and controversial that it is virtually useless.

Thus, the key pathophysiologic abnormality, the duodenal pH of patients with duodenal ulcer, has been noted to be more acid than normal (1), to be similarly near neutral (2), or similarly acid (3). If the duodenal contents in duodenal ulcer were, indeed, more acid than normal, this abnormality might be attributable to increased gastric secretion of acid. In this connection, it has been shown that the gastric secretory response to exogenous stimulants shows almost complete overlap between duodenal ulcer and "normal" individuals (4). The gastric secretory response to meals has been reported to be greater than normal (5), to be normal in magnitude but more prolonged than normal (6), to be normal (7) or greater than normal and more prolonged (8). If gastric secretion in patients with duodenal ulcer were proven to be greater than "normal," the cause might be a greater drive to secretion in these patients. It may

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therefore be relevant that gastrin levels after meals have been reported to be greater than normal in patients with duodenal ulcer, but also quite normal (4). In elaboration, it has been reported that only G34 gastrin and not G17 is released in greater than normal amounts in patients with duodenal ulcer (10), a finding which has also been denied (11). In a related manner, it has been reported that sham feeding releases gastrin in patients with duodenal ulcer but not in normal individuals (12), although it has also been shown that neither group manifests gastrin release, under these circumstances (13). Since the gastrin originates in the gastric antrum, it is relevant that it has also been reported that the antral content of gastrin and the number of antral G cells is less than normal in duodenal ulcer (14) or the same as normal (15) or increased (16). There may be some abnormality of the "feed-back" inhibition of gastrin release by antral acidification in patients with duodenal ulcer, resulting in less inhibition of gastric secretion than normal in these patients (17), a finding which has also been denied (18). Alternatively, the gastric parietal cells of patients with duodenal ulcer might be more sensitive than normal to stimulants. This type of increased sensitivity has been demonstrated (19) but also denied (20). Increased gastric secretion in duodenal ulcer might also be attributable to decreased gastric inhibition of some sort. For example, antral distension has been reported to inhibit the gastric secretory response to pentagastrin in normal individuals but not in patients with duodenal ulcer (21) while, conversely, it has also been shown that antral distension inhibits the gastric response to pentagastrin in patients with duodenal ulcer, but not in normal individuals (22).

Similar controversy surrounds the allegedly protective secretion of bicarbonate into the duodenum. Thus, it has been reported that the bicarbonate-secretory response to duodenal acidification is less than normal (4, 23), the same as (24) or greater than normal (25) in patients with duodenal ulcer. Basal levels of secretin are greater than normal (25, 26), the same as (27) or less than normal (28) in duodenal ulcer. The threshold for secretin release by acid is not different from normal (24) or higher than normal (29). The secretin response to duodenal acidification has been reported to be less than normal (18, 28), the same as (29) or greater than normal (25) in patients with duodenal ulcer.

The list goes on. Some of these differences have been attributed to "heterogeneity" of the patients with duodenal ulcer. It is obvious that there is heterogeneity, but it certainly is not obvious that the heterogeneity reflects differences in the pathophysiologic reaction of different types of patients, sufficiently significant to indicate different causes for the duodenal ulceration, (rather than merely denoting heterogeneity of the investigators and their techniques). In any case, no aspect of the pathophysiology of duodenal ulcer can be taken to reflect etiologic phenomena in our current state of confused knowledge.

It has long been held to be axiomatic that surgeons should reduce gastric secretory capacity to heal duodenal ulcers. Similarly, until recently, the pharmaceutical industry based its quest for ulcer-healing drugs on the criterion of gastric secretory inhibition, resulting in the admittedly successful invention of the H_2 receptor antagonists. Can we assume that these and other drugs heal ulcers by inhibiting gastric secretion, or neutralizing intragastric acid, or inactivating pepsin? Some of the many drugs that have now been shown to heal duodenal ulcer (30) do not have any of these effects. But even when a drug does in some way affect gastric juice or its secretion, is that why it heals duodenal ulcers?

In this connection, an excellent example of the conceptual and practical problems which may result from misinterpreting the successful therapy of duodenal ulcer is provided by the example of epidermal growth factor/urogastrone (EGF). This peptide heals experimental ulcers (31), an effect at first assumed to depend on the powerful gastric inhibitory properties of the peptide (32). However, as its name implies, EGF directly stimulates growth of cells involved in repairing wounds and ulcers (33), so that the ulcer-healing effect may be quite independent of gastric inhibition. In addition to these two quite separate effects, EGF increases mucosal resistance to trauma (34), perhaps by stimulating the production of extracellular glycoproteins and cell adhesiveness of fibroblasts (35). The peptide exerts yet a further effect–that of modulating viral replication (36). Since it has recently again been suggested that duodenal ulcer may be a manifestation of infection by viruses such as herpes simplex (37) (a suggestion which has been strengthened by the finding of high titres of antiherpes complex A viral antibodies in patients with acute exacerbations of duodenal ulcer (38)), clearly EGF may be exerting some quite unexpected effects in promoting healing of duodenal ulcers. The possibility is compounded by the recent report that cimetidine has been used effectively to treat infections with herpes simplex virus (39).

I conclude that conceptual fixation on gastric juice in consideration of the etiology of duodenal ulcer may be mistaken and advances in our understanding of the causes of the disease are likely to result from the study of factors only indirectly connected with gastric activity or, indeed, quite unconnected.

It is not surprising, therefore, that increasing attention has been paid recently to epidemiologic correlates of duodenal ulcer associations which have little or no obvious connection with gastric secretory function. For example, considerable emphasis has been placed on the long recognized (40) familial incidence of duodenal ulceration. A number of familial "markers" (41), such as hyperpepsinogenemia I (42) have been interpreted as reflecting a hereditary basis for the duodenal ulceration which affects members of several generations of some families. While the blood levels of pepsinogen have been reported to correlate with gastric acid-secretory capacity (43), we are not yet in possession of sufficient information to permit unequivocal inference of the "size of the stomach" from blood levels of pepsinogen, just as we do not calculate the size of the pancreas from blood levels of amylase. Indeed, until we know more about the origin of the circulating pepsinogen, it seems unsatisfactory to equate familial with hereditary. There are probably (or even certainly) environmental ulcerogens (infectious and chemical) with potentially strong familial incidence. The effects of these ulcerogens may depend not on any (obvious or recognized) hereditary "predisposition" to the infection (or chemical), but rather on an excessive environmental concentration of the infectious or chemical agent. Thus, the epidemiologic information about the markedly variable incidence of duodenal ulcer in Southern Asia (44) and the equally extraordinary recent increase in the incidence of duodenal ulcer (45) with shift of the Bantu population from kraal to town in South Africa (45) implies the action of environmental ulcerogens rather than hereditary factors (without in any way relating to gastric secretion).

Despite our apparent ignorance of the etiology of the duodenal ulcer, we seem to be approaching satisfactory medical control of the disease. I have reviewed the problems associated with the medical treatment of duodenal ulcer previously (46) and will only emphasize salient features or new developments.

Many of the groups of drugs which have now been shown to heal duodenal ulcers have no apparent similarities in pharmacologic properties, but all heal approximately 70 to 80 percent of duodenal ulcers in one month and most of the remaining ulcers can be healed by continuing treatment, or increasing the dose (at least when using H_2 receptor antagonists). The choice of ulcer healing therapy should, therefore, depend mainly on the avoidance of side effects during the course of treatment—a criterion which greatly favours H_2 receptor antagonists over other available drugs. It is worth emphasizing two other points. The high incidence of residual pain after healing of the duodenal ulcer, reported in some recent studies, indicates either a high incidence of oesophagitis (which is much more resistant to symptomatic relief and still much more difficult to treat satisfactorily than duodenal ulcer) or a high incidence of other, coincident disease which is primarily responsible for the upper abdominal symptoms (and which have therefore been incorrectly attributed to the duodenal ulcer). Such unsuspected disease (of the biliary tract, pancreas or intestine) must always be sought if there is residual pain when an ulcer has healed. Causes of nonhealing of ulcers include noncompliance, inadequate therapy and underlying diseases, ranging from the Zollinger-Ellison syndrome to conditions such as Crohn's disease. In addition, it has been reported that ulcers heal less well in smokers. We have recently found what may be an explanation for the unsatisfactory healing observed in some patients who smoke, since smoking seems to prevent the therapeutic inhibition of nocturnal gastric secretion (47). If gastric secretion is involved in the pathogenesis of duodenal ulcer (or reflects a situation permitting the occurrence of ulceration) then it is at night that the "noxious" effects of uncontrolled gastric activity are most likely to produce mucosal injury. Smoking should therefore be avoided after taking the nighttime dose of therapeutic drugs.

It has been repeatedly demonstrated that about 80 percent of ulcers relapse when treatment (with H_2 receptor antagonists) is discontinued after healing the ulcers (9, 30). It is worth permitting one such relapse, to define the 20 or so percent of individuals who tend to remain healed for long periods of time. The principal remaining therapeutic problem concerns the management of the patient after a successful second healing dose of one or other drug. Three methods of treatment have been used. "Demand treatment" involves self-administration of some drug (such as cimetidine) when twinges of pain are felt, usually for a day or two, until symptomatic relief is achieved. In a local trial, only ten percent of our patients specifically treated in this manner remained satisfied with their treatment after six months. The two other alternatives involve intermittent treatment, with repeated healing courses of the drug for symptomatic relapses or continuous maintenance treatment. It has been estimated (48) that with intermittent treatment, the likelihood of a patient having an active ulcer at any time is about one in ten and that each patient has about three clinical recurrences every two years. This type of treatment (using cimetidine) is about one quarter the cost of maintenance treatment but has the disadvantage of exposing the patient to the risk of frequent clinical reactivation of the ulcer, with potential complications and perhaps also an increased likelihood of pyloric stenosis following the repeated reactivation and rehealing. I would add that my patients receiving intermittent treatment tend to develop progressive hostility to the treatment and unwillingness to continue. The patients demand surgery and that, in my opinion, makes this type of treatment thoroughly unsatisfactory.

The therapy of choice is, therefore, prolonged maintenance treatment. The only drugs which have been satisfactorily tested for long-term treatment so far are the H_2 receptor antagonists. Maintenance treatment with nocturnal cimetidine or ranitidine seems safe and effective. Less than 20 percent of patients "break through" nocturnal maintenance treatment with either drug, so that there is a likelihood of recurrence every two to three years, or less. The recurrence can, of course, be healed by a full course of treatment and maintenance treatment can then be reestablished. The only problems of maintenance treatment are potential, or real, adverse reactions. In this connection, ranitidine seems at this time superior to cimetidine. During healing treatment, ranitidine is only required twice a day, compared with the five tablets of cimetidine which must be taken on four occasions during the day. As a result, compliance is significantly better with ranitidine. In the long term, cimetidine has an antiandrogenic effect (49) with increase in blood levels of testosterone (50) an effect which is not observed during long term treatment with ranitidine. Cimetidine also inhibits hepatic microsomal enzyme metabolism (51) with clinically significant effects on the metabolism and use of anticoagulants (52) and sedatives (53). Ranitidine does not have such effects. In addition, we have found that cimetidine significantly augments lymphocyte responsiveness, an effect which is also absent during treatment with ranitidine.

In my opinion, the most satisfactory method of managing duodenal ulcer at present is with one to two months' healing doses of ranitidine (150 mg twice daily) followed by maintenance treatment with 150 mg at night. Surgical treatment has now become largely irrelevant for uncomplicated ulcer disease and should be restricted to minimal interference, not resulting in irreversible anatomic alterations of the upper alimentary tract (that is, should be restricted to simple suture of perforations or oversewing of bleeding arteries). Any "definitive" operation for uncomplicated or complicated ulcers is unwarranted in most patients, in view of the attendant mortality and incidence of irreversible adverse effects, sequelae which have not been observed during the medical treatment of duodenal ulcers.

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Receptor-mediated Endocytosis: Review and Overview

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Abstract

On both sides of the plasma membrane, there are specialized structures that in a synchronized manner are responsible for the process of endocytosis. In contrast to phagocytosis, in which extensive areas of membrane and large amounts of cytoplasmic material are involved, pinocytosis comprises a very limited membrane area with a small number of molecules and a negligible amount of cytoplasmic mass. The importance of this process lies, therefore, on the number of times that it takes place on the overall surface of the plasmalemma. New information on the molecular events that occur beneath the lipidic bilayer resulted from the isolation of coated vesicles and characterization of the elemental components of the coat lattice. Here we describe work that contributed to our better understanding of the process of incorporation of essential molecules into the cell cytoplasmic environment.

One of the basic tasks a cell is confronted with is how to absorb the nutrients and regulatory molecules needed for growth and survival. Surprisingly little is known about this essential process called "endocytosis." In endocytosis, two varieties have been recognized: a generalized one (pinocytosis) in which small areas of plasma membrane invaginate, nonspecifically ingesting elements of the surrounding medium, using smooth vesicles (1, 2), and a specialized type (receptor-mediated endocytosis) in which cells take up specific macromolecules from the medium using coated vesicles (3).

Receptor-mediated endocytosis (Fig. 1) consists of: 1) binding of macromolecules to be internalized (usually proteins) to specific receptors on the surfaces of cells; 2) clustering of the protein (ligand) receptor complexes into many discrete patches–these clusters form over specialized structures localized to the cytoplasmic side of the plasma membrane called "coated pits"; 3) internalization of the ligand-receptor complexes into the cell via invagination of coated pits, forming coated vesicles; 4) processing of the content of coated vesicles by way of cellular metabolic pathways. Macromolecules absorbed through receptor-mediated endocytosis include polypeptide hormones, for example, insulin (4–8), epidermal growth factor (9, 10), nerve growth factor (11, 12), asialoglycoproteins (13–15), lysosomal enzymes (16), α_2-macroglobulin (17–19), and plasma transport proteins, such as low density lipoproteins (20–22), and transcobalamine II (23–25).

A common theme in cell biology is that specialization of function is accompanied by or dependent upon specificity of structure. The search for an understanding of basic cellular mechanisms is many times fruitful when studying cells performing a specialized task. Such a line of successful research has been carried out in cells distinguished by their ability to absorb specific large molecules to be utilized in the cytosol. This review will trace the significant advances made in the field of receptor-mediated endocytosis.

The story begins in the 1960's when electron microscopic techniques were becoming sophis-

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*This paper derives from Dr. Bloom's final year in the combined M.D./Ph.D. program, with Dr. Puszkin as **Thesis advisor.

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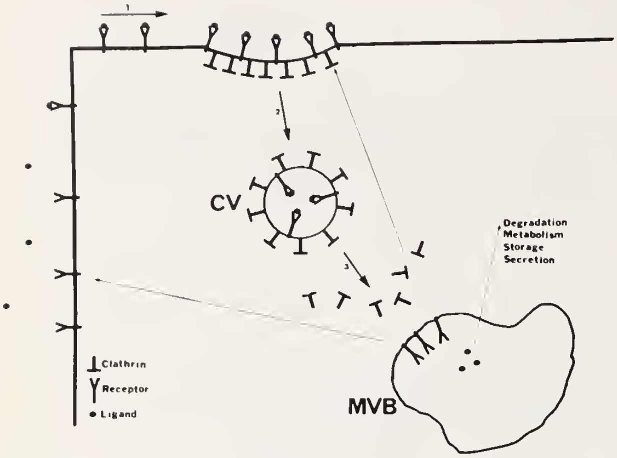

FIG. 1. Schematic representation of events leading to receptor-mediated endocytosis. *Step 1*: Ligand bound by receptor sites embedded in the membrane. These complexes aggregate over a coated pit. *Step 2*: Coated vesicle containing ligand-receptor complexes forms in the cytoplasm. *Step 3*: Fusion of vesicle membrane with a multivesicular body concomitant with depolymerization of the coat lattice. The coat lattice molecules will reassemble into a coated pit while membrane and receptor will be recycled into the plasmalemma.

ticated enough so that preservation and visualization of subcellular organelles were possible. In work dealing with normal cellular morphology, Porter (26), Fawcett (1), Palade (2), and Grey (27), noted areas of plasma membrane and also cytoplasmic membranous vesicles that contained bristles or coats on their cytoplasmic surfaces. It was believed that this coat material was proteinaceous and bound to discrete segments of membrane. The first clue regarding the function of these coated areas of membrane came from the work of Roth and Porter on the development of the mosquito oocyte (28). During the egg's resting state, the cortex of the oocyte was covered by many unoriented villi. At the base of the microvilli were shallow pit-like invaginations of membrane that had bristled spikes (coats) protruding into the cytoplasm. After incubating these eggs with yolk proteins–it was known from a previous study that these oocytes selectively absorbed certain yolk proteins (35)–large numbers of coated invaginations and coated vesicles formed containing these proteins. Such a change in morphology was absent in controls. It was hypothesized that the yolk proteins bound specifically to receptor sites on the membrane surface that had a juxtaposed protein coat underneath, on the cytoplasmic side of the membrane. Once receptor-ligand binding took place, the membrane invaginated and pinched off, forming coated, micropinocytotic vesicles. The coated vesicles coalesced to form large proteoid yolk bodies; the source of amino acids for embryonic development.

Later work gave support to this hypothesis (29–34). Rodewald was interested in the question of how animals acquired passive immunity (36). Young rats were known to absorb protective IgG from mother's milk through the gut. By studying the jejunal lining in 10-day-old rats, it was found that maternal rat IgG was selectively pinocytosed into the jejunal cells via coated invaginations at the base of the microvilli. The endocytosed IgG was transported via coated vesicles to the basolateral part of the cell and then exocytosed into the intercellular space. Immunoglobulins from other species and control serum proteins from the rat were not absorbed. Thus, it was apparent that these cells could selectively absorb certain macromolecules and that the absorption was mediated through a coated pit/coated vesicle uptake system.

As the electron microscopic evidence mounted for the involvement of coated vesicles in endocytosis, interest was directed to the biochemical properties of this uptake system. A major breakthrough was achieved in the mid-1970's by Pearse, with the development of a method for purification of coated vesicles from porcine and bovine brains (37) adapted from the work of Kanaseki and Kadota (38). By weight, the enriched fractions of coated vesicles contained three times more protein than lipid. Analysis of the protein content showed that there was one major species with a 180,000 molecular weight. This protein was named "clathrin," after the Greek *clathri*, meaning latticework.

Isolation of coated vesicles from widely varying cell types showed a remarkable homology in protein composition (39). Coated vesicles from rat, pig, rabbit and beef brains, bullock adrenal medulla, chicken oocytes and a lymphoma cell line all contained a major polypeptide representing approximately 75% of the total protein population with a 180,000 molecular weight (40–42). Researchers felt that clathrin was the sole protein of the coat surrounding the vesicles based on experiments in which certain buffers dissociated clathrin molecules from coated vesicles, while the other constituent proteins pelleted with the vesicle membranes (43, 44).

The striking homology of coated vesicle polypeptide composition correlated well with similarities in morphology. Regardless of tissue source, coated vesicle diameters consistently ranged from 600–1,000 Å. Electron micrographs of negatively stained coated vesicles showed the coat shell to be made of pentagons and hexagons arranged in polyhedral, latticed arrays (37–42). The coats forming closed shells around vesicles contained at least 12 pentagons ensured sufficient curvature for closure. The number of hexagons varied depending on the size of baskets formed. On cross section, the edges of the polygons appeared as spokes radiating from the central vesicle, and were 150 Å in length. Thickness of the edges of the polygons was approximately 50 Å. This morphology was remarkably consistent across species and cell types (Fig. 2).

Various workers were able to devise methods for isolating the clathrin species away from the vesicle membrane (44, 45). A study with highly purified clathrin showed that it was indeed the molecule responsible for forming the latticework of coated vesicles as in Figure 3 (45). The purified coat protein could form baskets reversibly or become dispersed in solution, depending upon the ionic conditions of the medium. Also, changes in turbidity and viscosity were noted (46). The most sensitive variable found to control clathrin basket assembly was the concentration of hydrogen and calcium ions, two strictly regulated cellular constituents (44, 45). Understanding the process of receptor-mediated endocytosis requires a complete elucidation of the biochemical and biophysical properties of the major protein involved, clathrin.

More recently, research has been directed at elucidating the dynamics of the coated vesicle uptake system *in vivo*. By combining morphologic, biochemical and immunocytochemical techniques, the actual molecular mechanisms of receptor-mediated endocytosis are being investigated.

Work on the low-density-lipoprotein uptake system in human fibroblasts has served as a prototype for understanding the initial ligand-receptor interactions (47). The binding of receptor to ligand appears to be specific. This obviously is an essential requirement for selective uptake. The surface of human fibroblasts contains 20,000–50,000 receptors for low-density lipoproteins at any given time (47). The receptors are proteins, and they require the presence of divalent cations for binding to occur. Mutations were identified in a group of patients with familial hypercholesterolemia wherein their fibroblasts, 1) bound less than 10% of the normal amount of low-density lipoprotein, or 2) exhibited no low-density lipoprotein binding at all. Functional low-density lipoprotein receptors play a vital role in cholesterol homeostasis (3). In the case of hormones and neurotransmitters, the idea of ligand-to-receptor specificity has long been recognized. The concept of a receptor should not be limited to its being a conveyor of information to a second messenger or a molecule which participates in neurotransmission. Receptors are involved also in the selective ab-

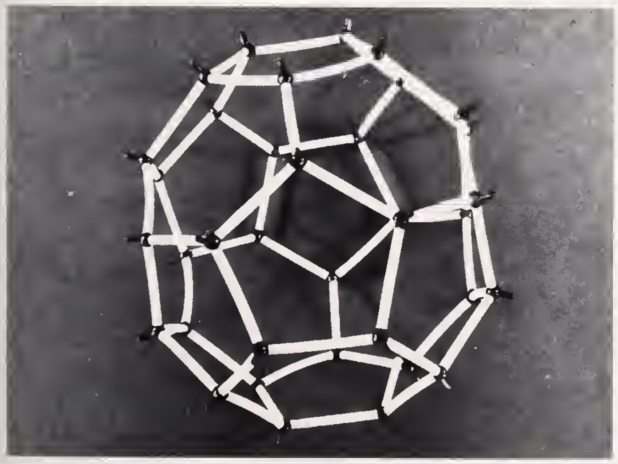

FIG. 2. Schematic representation of a typical lattice of clathrin molecules forming an icosahedral figure composed of pentagons and hexagons. Each side of a hexagon or pentagon constitutes an individual clathrin molecule.

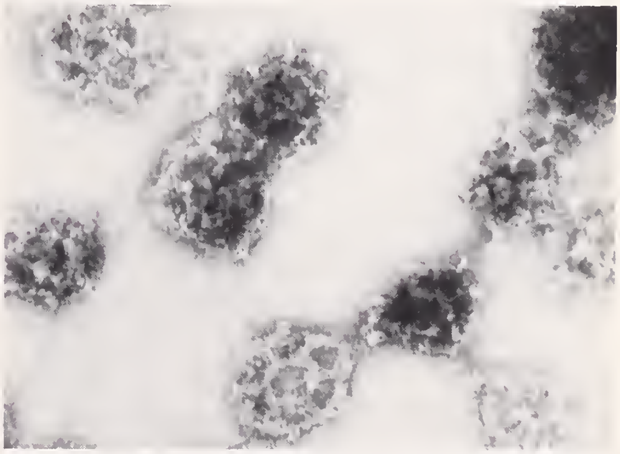

FIG. 3. Typical clathrin basket or cage formed *in vitro* by purified clathrin molecules when the pH of the solution is adjusted to 6.5. This preparation was stained with 1% uranyl acetate and viewed in the electron microscope. Magnification: 350,000×.

sorption of macromolecules directly into the cytosol.

Clustering of the ligand-receptor complexes over coated pits is a prerequisite for uptake into coated vesicles. In certain cells the unoccupied receptors are randomly scattered over the entire cell surface, and only after the ligand is bound will the occupied receptors cluster over coated pits. This clustering takes place in a matter of minutes and is prevented in the cold (6). Binding of ligand could induce a conformational change in the receptor which then would allow clustering to take place. Other cells have their receptors located over coated pits prior to ligand binding. A study using this type of cell line showed a mutant which exhibited binding, but there was no clustering over coated pits and no internalization (20, 48). This work implied that receptors have two functionally important sites: 1) a specific binding site, and 2) an internalization site, probably located intracellularly. In all cases, the receptors probably span the membrane.

The process of clustering may be controlled by certain enzymes called "transglutaminases" (47, 50). Extensive studies have shown that inhibitors of transglutaminases prevent clustering of various receptor-ligand complexes over the coated pit regions. Transglutaminases catalyze the formation of covalent bonds between lysine E-amino groups and the α-carboxyl group of glutamine in adjacent protein molecules. Theoretically then, by transglutaminase activity the ligand-receptor complexes may be held in coated pits by covalent aggregation of the cytoplasmic end of the receptors.

Another theory to explain clustering involves the concept of lipid flow mediated by actively endocytosing coated vesicles (51). The coated-pit-to-coated-vesicle process, by absorbing membrane, would set up a directional flow of lipid in the plane of the membrane toward the pits causing the receptor-ligand complexes to be swept towards and finally into the coated vesicles. Some assumptions made in this study have been corroborated by experimental facts (52, 53). It is known that in fibroblasts different macromolecules are clustered over and endocytosed into the same coated pits. Insulin, macroglobulin, and epidermal growth factor all cluster and enter fibroblasts through the same region of membrane (6). It is apparent that the coated pit uptake system functions as a generalized pathway of entry into cells.

Recent information concerning the biochemical makeup of coated pits may help explain certain aspects of clustering and internalization. The coated pit regions of the cell membrane have been shown in various studies to be distinct biochemically from the surrounding membrane. There is virtually no cholesterol in the phospholipid content of coated membrane (53). Since cholesterol is known to decrease membrane fluidity, an absence of this phospholipid could give the coated pit the flexibility and deformability needed for endocytosis. Coated pits have larger and twice as many intramembranous particles as seen by freeze-fracture, compared to the surrounding plasmalemma. Also, the coated regions behave like molecular filters since certain surface antigens present on all other parts of the plasmalemma are absent over the coated pits (52). It is possible that the coat protein recognizes these unique intramembranous particles and forms coated pits, and that an interaction between these elements and the ligand receptor complexes results in clustering and/or internalization.

A most dramatic and intriguing part of receptor-mediated endocytosis is the actual movement of coated membrane with the attached ligand-receptor complexes into the cytoplasm. One approach to understand internalization has been the study of the characteristics of clathrin, the major protein of the coated pit. As noted earlier, changes in pH and calcium ion concentrations can alter the structural conformations of the clathrin molecules from soluble, dispersed rods to polyhedral, lattice-like structures (44, 45). Recent work by Heuser using extremely rapid freezing captured the clathrin molecules, forming progressively more curved lattice structures, which could explain the actual invagination of attached membrane. This exciting finding constitutes a major contribution to the understanding of the molecular mechanism of endocytosis (54). By the technique of immunofluorescence, workers conclusively showed that clathrin was located under the membrane in a discrete dotted pattern along the surface of the fibroblast (55), as in Figure 4. The dotted pattern which represents coated areas of membrane was aligned with the fibroblasts' microfilamentous network. This fact, along with other binding studies, points to an association between coated pits and actin filaments in the fibroblast (45). Compounds which destroy microfilaments also

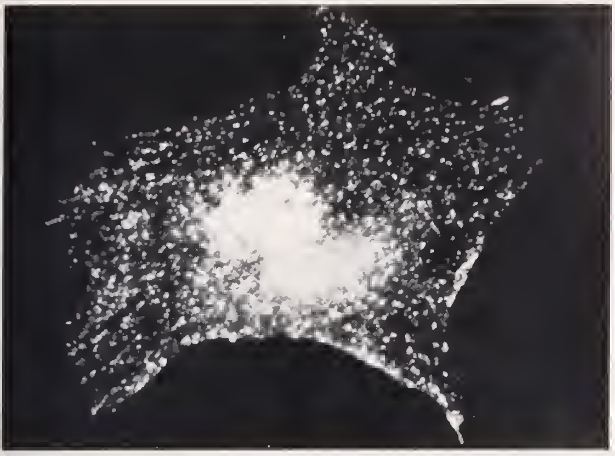

FIG. 4. Fibroblasts in culture stained by indirect immunofluorescence with clathrin antibodies. A typical pattern of linearly arranged dots is found with patches of intense fluorescence in a perinuclear position. Magnification: 2,300×.

prevent internalization (56). It is hypothesized that an interaction between clathrin and the cytoplasmic contractile proteins is involved in the vectorial movement of coated vesicles into and throughout the cytoplasm.

The fate of the receptor-ligand complexes after internalization depends on the cell type studied and the macromolecule absorbed. In the original case of yolk protein absorption, the ligand was stored in vacuoles for use later in the cell's development. With the absorption of rat maternal IgG, the ligand was internalized, secreted into the intercellular space, and eventually taken up by the bloodstream yielding neonatal passive immunity. In the low-density-lipoprotein uptake system, the ligand is endocytosed, then transported towards lysosomes for degradation and metabolic utilization. With various polypeptide hormones, uptake is followed by degradation or transport to other organelles for further molecular interaction. In most of these systems receptors are recycled to the plasmalemma after ligand processing is initiated (57, 58). The exact molecular mechanism of receptor recycling awaits elucidation.

Receptor-mediated endocytosis gives cells a powerful tool for controlling their environment. By using a ligand-specific receptor, a cell specialized in a certain metabolic pathway can selectively and efficiently absorb from its surrounding milieu–which contains hundreds of different types of molecules–that one species destined to be metabolized. By aggregating, internalizing and processing hormone receptor complexes, a cell can regulate hormonal action. Internalization and degradation of a hormone will terminate its action. By controlling the number of receptors available, the cell regulates its degree of interaction with circulating molecules. Thus, further investigation of the molecular mechanisms of endocytosis must still be carried out. To understand endocytosis would be to understand one of the cell's most basic and important functions.

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Brain Clathrin: Ultrastructural and Biophysical Evidence of Reversible Assembly

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Abstract

Brain clathrin, a polypeptide involved in endocytosis, was isolated from an enriched fraction of cerebral cortex coated vesicles. The protein assembled *in vitro* cages or basket structures that resembled those on coated vesicles. Assembly was dependent on pH, ionic strength, and independent of cations and ATP. Upon formation of baskets at pH 6.5, clathrin solutions became turbid and less viscous. These parameters were reversed by increasing the pH back to 7.5, at which time clathrin solutions became clear and viscous. These changes correlated with the assembly and disassembly of cages or baskets viewed by electron microscopy. These properties may help to elucidate clathrin's role in the process of endocytosis.

Introduction

Receptor-medicated endocytosis is a process in which specific macromolecules (metabolites and regulatory proteins) are absorbed intact by cells (1). This process allows cells to regulate their environment in an efficient and selective manner. It is believed that receptor-mediated endocytosis occurs via invagination of specialized segments of plasmalemma called coated pits (2). The coat a) is located on the cytoplasmic side of the membrane, b) is proteinaceous, and c) is predominently one protein species, clathrin, with a 180,000 molecular weight (3). After invagination, the coated pits convert into coated vesicles which eventually may fuse with lysosomes as well as with other organelles and, in the process, lose and reutilize their coat material. It is apparent that the molecules of the protein coat have the ability to assemble and disassemble at various stages of endocytosis (4). By studying the structural and biophysical properties of clathrin, the molecular mechanism that governs the various states of coat assembly can be elucidated (5).

We describe within, the purification of clathrin from bovine brain coated vesicle fraction. The purified clathrin molecules were found capable of assembling stable structures that resembled closely those on coated vesicles. Furthermore, upon assembly and disassembly we determined changes related to various states of clathrin's molecular polymers that are compatible with observations of its morphology *in vivo.*

Materials and Methods

Clathrin Purification

Bovine brains were delivered fresh in ice from a local slaughterhouse. The brains were cleansed of meninges and the grey matter separated from the white matter by suction. The grey matter from three bovine brains was homogenized by three, ten-second bursts at one-minute intervals using a Waring blender at top speed, with 400 ml of 0.1 M Tris-HCl, pH 7.0, containing 1 mM EGTA, 0.5 mM $MgCl_2$, 1 mM 2-mercaptoethanol and 0.02% sodium azide. The homogenate was

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centrifuged at 30,000 × g for 30 minutes, the supernatant decanted, and further centrifuged at 100,000 × g for 60 minutes. This crude, coated vesicle pellet was extracted by 10–12 strokes of a Teflon glass homogenizer with 50–100 ml of 0.02 M Tris-HCl, pH 7.5, containing 1 mM 2-mercaptoethanol, 1 mM EDTA, 0.02% sodium azide and left standing at 4° C for 16 hours. The crude coated vesicle extract was centrifuged at 100,000 × g for 60 minutes to remove membrane fragments. The supernatant was made 30% saturated in ammonium sulfate by addition of solid crystals and the pellet obtained after centrifugation at 15,000 × g suspended in 20 mM Tris-HCl, pH 7.5, 1 mM 2-mercaptoethanol, 1 mM EDTA, 0.02% sodium azide. This material was dialyzed against the 20 mM Tris buffer, pH 7.5, now containing 2 M urea, and 10 ml of the protein solution (8–10 mg/ml) loaded on top of a Sepharose 4B column, 2.5 × 90 cm. Proteins were eluted with the same 2 M urea-Tris buffer. Eluting fractions were monitored by absorbance at 280 nm, the protein peak II pooled and concentrated by 50% ammonium sulfate precipitation (5). The pellet was resuspended in a small volume of 2 M urea-Tris buffer and rechromatographed on a similar Sepharose 4B column. The peak II from the second column was concentrated and dialyzed against 20 mM Tris-HCl, pH 7.5, 1 mM 2-mercaptoethanol, 0.02% sodium azide and run on Sepharose 4B column eluted with same buffer. The material that eluted in the first peak represented purified clathrin. It was concentrated, dialyzed and stored frozen at −20° C in 10% sucrose.

Sodium-dodecyl-sulfate Polyacrylamide Gel-electrophoresis

Single cylindrical gels of 7.5% polyacrylamide were prepared. Protein samples (25–100 μg) were loaded on top of the gels and an electrical current was applied for about 16 hours until the tracking dye reached the gel bottom. Proteins were solubilized in 1% sodium-dodecyl-sulfate and reduced by 0.1% 2-mercaptoethanol before application to the gel. The gels were fixed in 45% methanol, 7% acetic acid and for two hours at 37° C, stained with 0.5% Coomassie blue, and destained by diffusion in 7% acetic acid, 5% methanol (6).

Protein Determination

Total proteins were estimated by the Lowry method using bovine serum albumin as the standard (7). Samples were prepared in triplicate, and the absorbance read at 750 nm in a Beckman spectrophotometer.

Electron Microscopy

For negative staining, 10 μl of a clathrin solution (5 mg/ml) was mixed with 90 μl of appropriate buffers, left standing for one hour at room temperature and at 4° C overnight. Aliquots (4–5 μg of total protein) were placed on Formvar carbon-coated grids for 20 seconds, drained, stained for two minutes with 1% uranyl acetate, air-dried and examined in a JEOL JEM 100B electron microscope at 80 Kv. In some experiments, the diluted clathrin solutions were placed immediately on the Formvar carbon-coated grids.

Sucrose Gradient Centrifugation

Discontinuous gradients in volumes of 5 ml each of 10%, 20%, 30%, 40%, 50%, 55%, and 60% sucrose dissolved in appropriate buffers were prepared. Approximately 1–2 ml of clathrin assembled as baskets at pH 6.5 in 20 mM Tris-HCl at a concentration of 3–4 mg/ml were layered gently on top of the gradients and centrifuged in a swinging bucket rotor SW 27 at 27,000 rpm in a Beckman ultracentrifuge for 16 hours at 4° C. Gradients were fractionated with the aid of a peristaltic pump into 1-ml aliquots, and protein concentration estimated by absorbance at 280 nm.

Turbidimetric Determination

Clathrin's turbidity was measured at 425 nm using a Beckman model 25 recording spectrophotometer at room temperature. Clathrin in solution was pumped continuously through a microflow cuvette using a peristaltic pump (Buchler Instruments) from a reservoir of about 3–4 ml of fluid stirred gently with the aid of a magnetic bar and electromagnetic stirrer wherein a combination electrode monitored pH changes. The pH was adjusted by addition of calibrated volumes of 0.4 M MES buffer, pH 6.0, or 0.5 M Tris-HCl, pH 7.5. At selected pH values, samples were withdrawn for viscosity measurements, and negative staining electron microscopy.

Viscometric Determination

An Oswald viscometer with a capillary flow time of 335 seconds for distilled water was used.

Viscometric determinations were performed in a constant temperature bath at 25° C. At each pH change, a sample was removed for electron microscopy. Protein aggregates that occasionally formed as a result of the passage of clathrin through the capillary tube were removed by centrifugation at 37,000 × g for ten minutes to prevent clogging of the viscometer. The values showing viscosity changes of clathrin as a function of concentration were obtained by gradual dilution and clarification by centrifugation at each determination point.

Results

Clathrin Purification

The purification of clathrin by column chromatography resulted in a protein solution whose polypeptide composition is illustrated in Figure 1. The major polypeptide migrated with an electrophoretic mobility of 180,000. Densitometric scan at 550 nm revealed that the clathrin was over 95% pure.

Basket Assembly

Highly purified clathrin was used to elucidate its assembly/disassembly characteristics. Since coated vesicles were stable through the isolation and fixation procedures, it was felt that *in vitro* reassembly of clathrin into coats and their visualization should be feasible. Parameters such as pH and ionic strength were varied in an attempt to find the conditions affecting clathrin's polymerization characteristics.

The effect of hydrogen ion concentration was analyzed. For this, clathrin preparations were viewed after uranyl acetate staining in the electron microscope. Regardless of the buffer used (Table I) at pH 7.2–8.0, clathrin molecules were polydispersed with rod-like shapes. No structures resembling the coat of coated vesicles were observed (Fig. 2).

Since coated vesicles were isolated initially using a buffer composed of 0.1 M MES, pH 6.5, this buffer was used in an attempt to reproduce conditions that favored coat structure assembly. Figure 3 shows the effect produced by lowering the pH from 7.5 to 6.5. Highly purified clathrin formed empty baskets or cages morphologically similar to the coats on vesicles isolated directly from tissue, except that these *in vitro* cages contained no membrane. The basic units of pentagons and hexagons arranged as cages or baskets was evident. The dimensions of these baskets (600–1,000 Å in diameter) were within the range of coated vesicles reported in the literature (8). Over the pH range 6.0–6.8 for all buffers tested, baskets were the predominant structure formed. In the pH range 6.9–7.1, both baskets and depolymerized clathrin were present. This pH range appeared to be a zone of transition between the two forms of clathrin since neither structure was predominant.

When the pH of the solutions containing baskets was raised back to pH 7.5, the baskets disappeared and were replaced by dispersed clathrin and bundles of filaments (apparently linearly arranged clathrin molecules, Fig. 4).

TABLE I
Effects of pH on Baskets with Different Buffers

		Amorphous Aggregates	Baskets
Tris Maleate	pH 6.2–6.8	−	+
	pH 6.8–7.2	±	±
	pH 7.2–7.6	+	−
Cacodylate	pH 6.2–6.8	−	+
	pH 6.8–7.2	±*	±
	pH 7.2–7.6	+	−
MES	pH 5.5–7.0	−	+
	pH 7.2–7.5	+	−
Tris	pH 7.0–8.5	+*	−
Glycine	pH 3.0	+	−

* Filamentous structures were present.

FIG. 1. Sodium-dodecyl-sulfate cylindrical gel of 7.5% polyacrylamide loaded with highly purified clathrin, after a third run on a Sepharose 4B column. Gel scan densitometry showed the preparation to be over 95% pure.

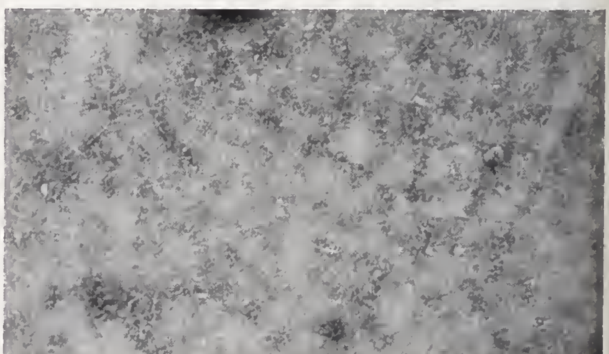

FIG. 2. A negatively stained preparation of clathrin suspended in Tris-HCl buffer, pH 7.5. In this preparation we observe clathrin molecules of rod shapes dispersed in solution. Partially formed polygonal structures are seen. Magnification: 120,000 ×.

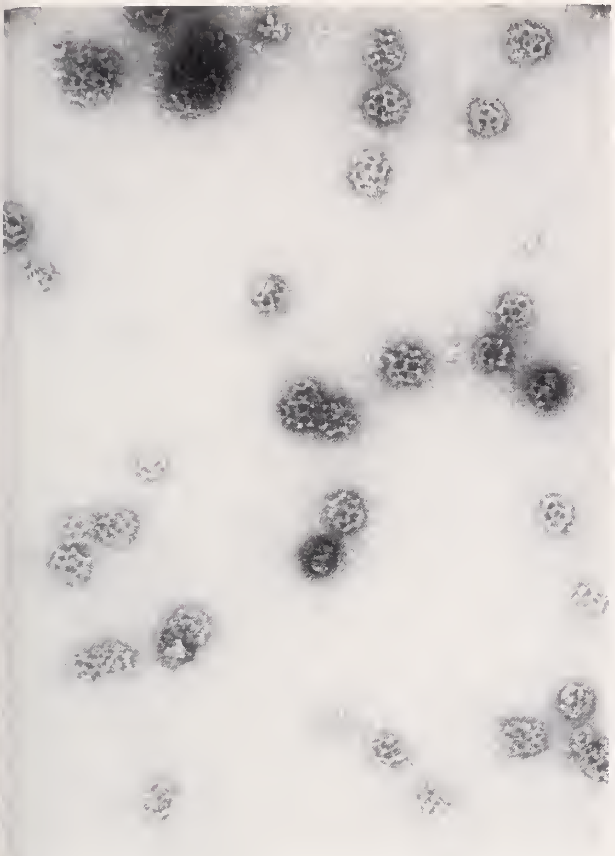

FIG. 3. This picture shows the unique formations of clathrin assembled when the pH is reduced from 7.5 to 6.5. These structures were negatively stained and are apparently formed by pentagonal and hexagonal units joined together forming an isocahedral structure. Magnification: 120,000 ×; Inset magnification: 250,000 ×.

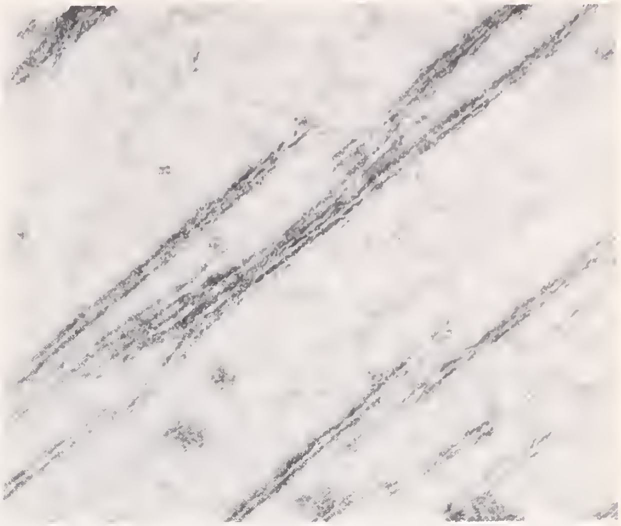

FIG. 4. Negative staining of clathrin preparation after pH was raised from 6.5 to 7.5. No baskets are seen, but filaments of clathrin predominate. Magnification: 120,000 ×.

Cross-linking of filaments within the bundles and between separate bundles was observed. If this clathrin preparation was dialyzed against a Tris-HCl buffer, pH 7.5, containing 2 M urea, the filamentous bundles disaggregated. After dialysis to remove urea and high speed centrifugation (150,000 × g for 60 minutes) to remove some aggregated proteins, the supernatant was composed essentially of monodispersed clathrin. Lowering the solution's pH, clathrin again formed baskets. These steps could be repeated several times with identical results.

The effect of various ionic conditions on basket formation was investigated and the results summarized in Table II. Apparently, neither calcium nor magnesium ions were required for basket formation since addition of EGTA and EDTA (0.1–1.0 mM) had no effect on assembly of cage structures. However, $CaCl_2$ concentrations above 200 mM and KCl above 500 mM completely inhibited basket formation. Basket formation was prevented by 2 M urea; an expected finding, since this was the concentration used to dissociate clathrin from membrane prior to column chromatography.

Stability of Baskets

Sedimentation in discontinuous sucrose gradients was used to investigate the effect of ionic conditions on pre-formed basket structures. The control gradients consisted of discontinuous layers of 10%, 20%, 30%, 40%, 50%, 55%, and 60%

TABLE II

Effects of Ionic Conditions on Basket Formation

		Amorphous Aggregates	Baskets
$CaCl_2$	EGTA	−	+
	10 mM	−	+
	50 mM	−	+
	100 mM	−	+
	200 mM	+	−
$MgCl_2$	EDTA	−	+
	10 mM	−	+
KCl	50 mM	−	+
	100 mM	−	+
	200 mM	−	+
	500 mM	+	−
ATP	0.1 mM	−	+
	1 mM	−	+
	5 mM	−	+
	10 mM	+	−
Urea	2.0 M	−	−
SDS*	2.0%	−	−

* Sodium-dodecyl-sulfate

sucrose dissolved in 0.1 M MES, pH 6.5, the buffer system favoring basket structures.

Under control conditions, that is, 0.1 M MES, pH 6.5, clathrin structures banded at the 50%–55% interface (Fig. 5, top). The presence of 2.5 mM EDTA in all sucrose layers had no effect on this pattern. Sucrose gradients prepared with 0.5 M KCl or 20 mM Tris, pH 7.8, showed markedly different sedimentation patterns (Fig. 5, middle and bottom). Most protein equilibrated at the 20%–30% interface, with smaller amounts at the 40%–50% interface. Sodium-dodecyl-sulfate polyacrylamide gel-electrophoresis confirmed that the protein absorbance was due to a 180,000 molecular weight species.

Examination of aliquots from the gradients by negative staining was performed to analyze the type of clathrin assembly. The electron micrographs showed that baskets were present in the control and EDTA containing gradients only at the 50%–55% interface (called the basket zone). The proteins sedimenting at the 20%–30% interface in both the 0.5 m KCl, pH 6.5, and 20 mM Tris, pH 7.8, sucrose gradients appeared either polymerized as filaments of various widths or aggregated. The protein at the 40%–50% interface showed amorphous clathrin aggregates. There were no baskets in any segment of these gradients and, furthermore, the basket zone was devoid of protein. It was apparent from these experiments that the preformed baskets were sensitive to various ionic conditions and had disassembled. High pH (7.8) and KCl concentration (0.5 M) caused the baskets to disassemble into filaments and aggregates. The extent of disassembly was reflected in its different sedimentation patterns.

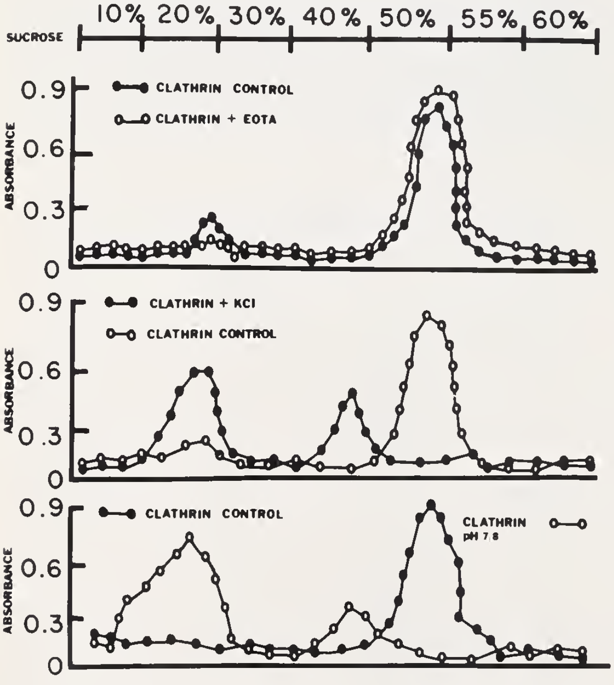

FIG. 5. Centrifugation of clathrin on sucrose gradients. Absorbance was measured at 280 nm, while fractions were being withdrawn from the gradient. The top figure shows clathrin assemblies sedimenting at the 50%–55% sucrose interface. Both the control and EDTA sucrose gradients show similar sedimentation patterns. The middle graph was obtained with clathrin on a sucrose gradient containing 0.5 M KCl. The lower graph shows the effect of sedimenting clathrin as baskets or cages in a sucrose gradient with a Tris-HCl buffer of pH 7.8.

Reversibility of Clathrin Assemblies Determined by Turbidity

The turbidimetric changes found by varying the ionic environment of purified clathrin solutions were monitored with a recording spectrophotometer at 425 nm. When the pH was lowered from 7.2 to 6.0, turbidity increased (Fig. 6). The turbidity change was rapid and reached a plateau value within one minute over a protein concentration range of 1.0–4.0 mg/ml. Raising the pH above 7.2, turbidity decreased rapidly to control values. When pH was lowered again, turbidity increased. To determine which structures were responsible for such changes, aliquots of clathrin's solution at various pH's were examined electron microscopically. Clathrin as baskets consistently presented optically opaque solutions (pH 6.0–6.8). Colchicine (0.25 mM) had no effect on the turbidity profiles, therefore diminishing the possibility that small amounts

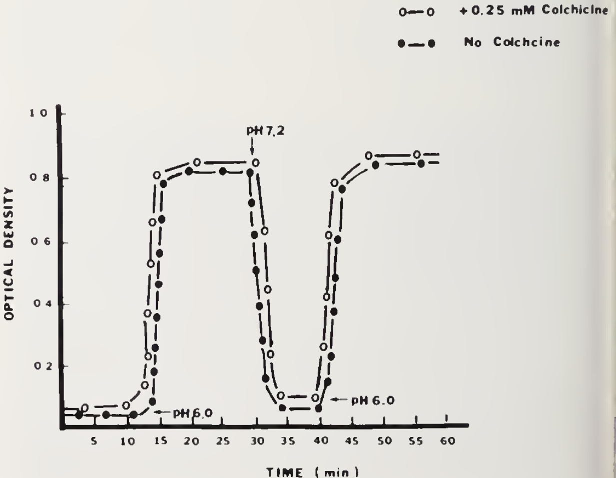

FIG. 6. Changes in optical density by adjustment of pH of a purified clathrin preparation. An increase in turbidity is observed when the pH is adjusted to 6.0. This figure illustrates the reversibility of turbidity by a sequential adjustment of pH from 7.2 to 6.0, and vice versa. There is no difference in the pattern upon addition of 0.25 mM colchicine.

of contaminating tubulin were contributing to the turbidity changes noted. When 0.5 M KCl was added before basket assembly occurred, small turbidity changes occurred by lowering or raising pH. On the other hand, the addition of 0.5 M KCl after basket assembly had occurred (at high turbidity values) caused turbidity to drop significantly.

Reversibility of Clathrin Assemblies Measured by Viscosity

Viscometric measurements of various clathrin solutions were performed to establish a possible correlation between reversible basket formation and changes in viscosity. The reduced specific viscosity of clathrin in solution as a function of concentration is illustrated in Figure 7 by the line connecting the open circles. Reference to the reduced specific viscosity obtained at various protein concentrations established that a significant drop in viscosity also occurred by adjustment of pH to 6.5 or 6.0. The results obtained by adjusting the pH of two different preparations of clathrin at various starting protein concentrations are shown. In all instances, a drop in viscosity was observed when the solution's pH was decreased. Viscosity returned to initial values after the clathrin solution's pH was raised back to its original point. Viscosity changes were evident as soon as the sample was transferred from the pH meter to the viscometer and a measurement made, usually one to two minutes after adjusting the pH. Morphologic correlation to the viscometric changes also were monitored by electron microscopy. Low pH, low viscosity solutions showed many baskets, while high pH, high viscosity solutions revealed a mixture of polydispersed protein molecules, occasional filaments, but no baskets.

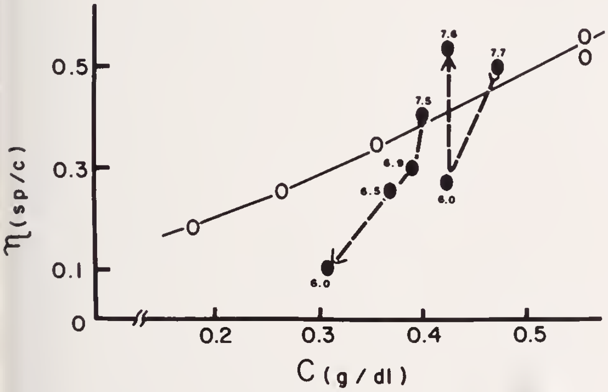

FIG. 7. A plot of specific viscosity as a function of concentration. A normalized curve joined by the open circles denotes the changes in specific viscosity at different protein concentrations. The dark circles joined by the dashed line indicate a given preparation of clathrin whose pH was changed. In one sample, the pH 7.7 value of viscosity is indicated and the drop in viscosity occurs below the normalized line when the pH is reduced to 6.0. Viscosity increased above the normalized line when the pH was returned to 7.7. Another clathrin preparation illustrates viscosity changes at intermediate points in the adjustment of pH: 7.5, 6.9, 6.5 and 6.0.

Discussion

Previous studies have shown that the receptor-mediated endocytotic system via coated vesicles is dynamic in nature, with movement of membrane elements between the cell surface and internally located organelles (9, 10). Therefore, such a system would require protein molecules that could form a lattice or coat which could assemble and disassemble in a highly efficient and controlled manner. In this study, we showed that clathrin, the major coat protein, has biophysical properties compatible with its hypothesized function in the cell.

The formation of basket structures *in vitro* by the purified clathrin molecules is most significant. That clathrin molecules themselves have the ability to form cages morphologically identical to those found *in vivo* implies that clathrin is the basic building block of the coat lattice (8). The assembly of clathrin varies as a function of pH and ionic environment. At a pH lower than 7.0, the surrounding proton charge apparently favors clathrin to attach at either end of its elongated molecules forming the basket lattice and its closure. When the pH is above 7.0, clathrin molecules dissociate or attach lengthwise, disrupting the overall cage structures as well as the hexagonal or pentagonal subunits (Fig. 8).

In addition to pH, ionic strength influenced the configuration of clathrin assemblies. Clathrin, in the presence of 0.5 M KCl at pH 6.5, did not form cages with the distinct appearance typical of those formed in the absence of salt. The presence of ionized salt possibly altered distribution and molecule interaction. Since pH and salts affected clathrin assembly, it can be stated that basket formation is ionic dependent and not covalent in nature. This type of chemical interaction for clathrin is useful at least for two reasons. Cells can control their ionic environment through ion exchange pumps or ionic gradients between subcellular compartments. The pH range of 6.8–7.2, which is critical for determining clathrin structural formations, is probably within the intracellular pH capabilities of most cells (11). Also, ionic interactions are much weaker than covalent bonds. A re-

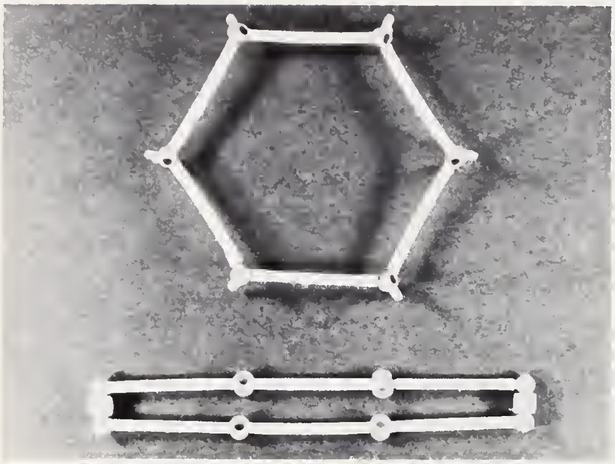

FIG. 8. Model of two types of clathrin assemblies. The top configuration represents the basic hexagonal unit probably made of 6 or 12 clathrin molecules if dimers exist. The hexagonal arrays exist at low ionic strength with pH's below 7.0. The bottom figure represents a filament segment composed of clathrin molecules. Theoretically the hexagon can collapse into the filament as the pH is raised above 7.0.

versible assembly system would require the flexibility inherent in noncovalent linkages.

The ionic nature of basket assemblies was confirmed by the changes noted in sedimentation rates of clathrin lattices in various sucrose gradients. To determine conditions that affected the stability and shape of clathrin baskets, they were subjected to centrifugal forces and their sedimentation parameters analyzed on sucrose gradients where pH and salt concentration could be controlled. The high salt or high pH (7.5) gradients both caused pre-formed baskets to disassemble. Apparently, these ionic environments overcame the protein/protein interactions between the clathrin molecules in the baskets. The clathrin molecules rearranged into two populations: one of high density (aggregates), and the other cross-linked filaments of light buoyancy. The reversibility of these structures found with such experiments fits well with the hypothesized role of clathrin in coated vesicle dynamics.

The high reactivity of clathrin molecules becomes evident during polymerization as evidenced by the almost instantaneous turbidity and viscosity changes noted upon varying the ionic environment. The turbidity changes correlated well with the state of clathrin configurations. Decrease in turbidity occurred with simultaneous disappearance of baskets and the appearance of filaments. The basket- or cage-like formations of clathrin produced a light-scattering effect with the resultant increased turbidity. All conditions which caused basket disassembly also caused a decreased turbidity when tested. Thus, changes in basket assembly can be monitored by following the solution's turbidimetric profile. This became an efficient tool for studying clathrin's unique structural properties. The reversible changes of clathrin's turbidity point to a reversibility of basket formation and breakdown.

The finding that clathrin solutions exhibited intrinsic viscosity suggests that the asymmetrically shaped molecules, the axial ratio of which is approximately 2.7 (unpublished data), polymerized into reticular or linear structures as some other structural proteins do, for example, tubulin, actin, myosin, tropomyosin. This postulate proved to be correct when the protein solutions were examined by electron microscopy with negative staining and filaments were found. The reduction of pH from above 7.0 to 6.5 was accompanied by both basket formation, and a decrease in viscosity. When assembled as baskets, clathrin molecules offered reduced viscosity, probably because of less frictional resistance or diminished shear force during their passage through the viscometer's capillary tube. The reversible viscometric properties of clathrin point to the coat protein's ability to form certain configurations in association with a changing ionic milieu. It is possible that, *in vivo*, a local change in viscosity in the area of coated pits could assist in membrane deformation or invagination.

If extrapolation of clathrin properties determined *in vitro* apply to their presence and behavior in the cells' cytoplasms, then when the proper stimuli and proton environment are provided, clathrin may form baskets around a given membrane area, constricting it, thus inducing the formation of a coated vesicle. The coat of these vesicles seems sturdy for these functions, surviving the effects of high centrifugal forces, fixation and staining needed for their visualization at the electron microscope. Thus, a vesicle protected by a lattice may be resistant to stresses and premature fusion with the abundant cytoplasmic cisternae. A far-reaching consequence of clathrin's newly described properties is that this particular protein could interact *in vivo* with the actin cytoskeleton (12). In this way, the coated vesicle may arrive at its proper destination, possibly near the nucleus, where a neutral pH could disassemble the lattice permitting the vesicle to fuse. Undoubtedly, future work will elucidate precisely the overall role of clathrin in the living cell.

Acknowledgments

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Opsoclonus and Oscillopsia

Peter Herman, M.D.

Abstract

Four cases of oscillopsia and opsoclonus are described. One patient developed opsoclonus and oscillopsia as one of the earliest manifestations of lymphoma. The other patients had multiple sclerosis as judged by the clinical course and spinal fluid findings.

The association of opsoclonus and oscillopsia are characterized by: 1) continuous rapid eye movements; 2) direction and amplitude of each eye vary; 3) if the ocular globes appear still, there is retinal nystagmus; 4) visual acuity is usually decreased; 5) on closing one eye, vision is usually improved; 6) the images usually disappear when closing the eyes.

In cases with worsening visual acuity, an underlying carcinomatous disease should be ruled out. Steroids are helpful. Clinically, the lesions responsible for opsoclonus and oscillopsia appear to be multiple and localized mostly in the cerbellum and brain stem.

Four patients with oscillopsia and the abnormal eye movements producing them are described. Oscillopsia is defined as an imagined movement of a stationary object caused by a rapid, irregular, uncontrollable eye movement. Oscillopsia is not rare. One author has observed at least 35 cases over the last 16 years (1). The visual disturbances are variously described by patients as: "eyes not focusing," "poor eye sight," or "double vision." Often, patients state that objects appear to be "shimmering," "jumping," or "dancing" (2–4). The eye movements causing oscillopsia are variously called oscillating eye movements, opsoclonus, jerking eye movements, flutter and spontaneous nystagmus, and are used interchangeably in the literature as well as in this report.

Oscillopsia almost always results from pathology affecting the central nervous system (CNS) (5–10), but has little localizing value (2). The cerebral hemispheres, deep gray nuclei, brain stem, and vestibular system may all be implicated separately or simultaneously, but lesions in the cerebellum are most frequent (2, 5–7, 9). Demyelinating disorders followed by encephalitis, particularly the variety affecting the brain stem (2, 4, 10–13) are the most common offenders. In the past, streptomycin was often incriminated (2, 14). The aminoglycosides which significantly affect the eighth cranial nerve have a predilection for the cochlear branch (14–16) and, in spite of their widespread use, these drugs have not been reported t cause oscillopsia (8–10). Amongst other drugs, only one case of oscillopsia secondary to Dilantin use was reported (2). In recent years, opsoclonus and oscillopsia have been described i association with early stage neoplasms. On case of opsoclonus has been reported with carcinoma of the breast (7). Another preceded th clinical manifestation of lung carcinoma (8). A few case reports of neuroblastoma in children initially presenting with opsoclonus are o record (17, 18). In one of our patients (Case #3) oscillopsia was an early symptom of a protracted disease which proved to be a fatal lymphoma. Since some of these diseases, such a neuroblastoma and lymphoma are amenable t treatment early in their course, prompt searc for causes of oscillopsia is important.

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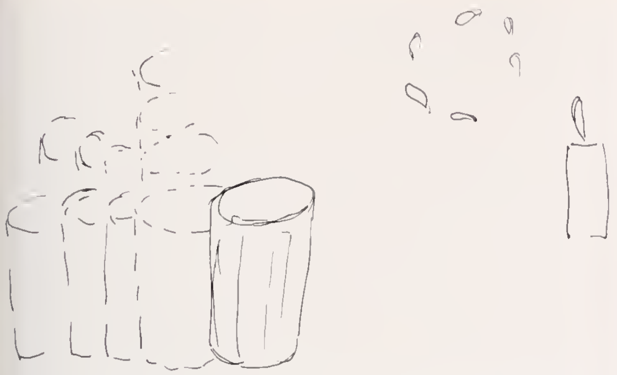

FIG. 1. Exact reproduction of a "still" visual image as seen by Patient #1.

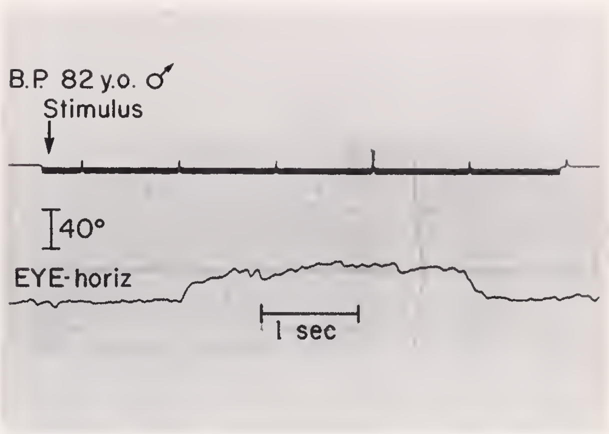

FIG. 2. Notice small amplitude eye movements. E.O.G. recording in Patient No. 3.

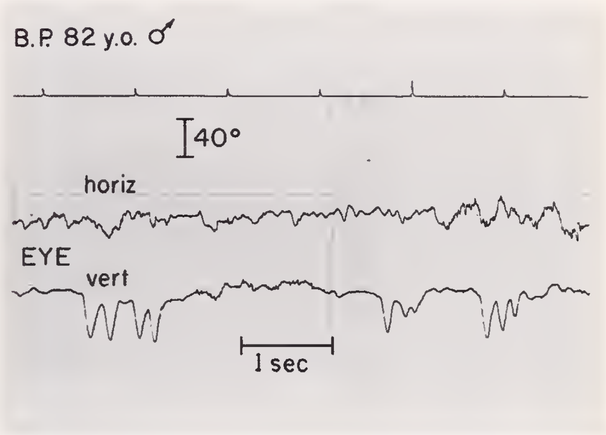

FIG. 3. Same patient three months later. Notice increase in amplitude of eye movements and the presence of vertical movements.

Materials and Methods

Four patients recently admitted to The Mount Sinai Hospital were examined. All had CNS disease and were known to have oscillopsia of several years duration. The pertinent data of thirty-one patients of whom fifteen were reported elsewhere (2) were analyzed.

Electrooculography was performed in the usual manner with silver-silver chloride electrodes applied to the outer canthi of the eyes recording the conjugated horizontal movements, and a frontal electrode as reference. Silver-silver chloride electrodes placed above the eyebrow and below the eye globe at midpoint recorded the left eye vertical movements.

The recording of the horizontal and vertical eye movements was simultaneous. Rotatory movements, although present, cannot be seen on the recording. The eye movements were recorded by a Grass model T5 4-channel polygraph, in room light and, on a few occasions, in darkness. Calibration of the eye movement amplitude was done prior to the beginning of the recording so that ten millimeters on paper equal 40 degrees of eye deviation in the horizontal as well as vertical plane. (Figs. 2, 3).

Case Reports

Case #1: (F.S.)

The patient was a 30-year-old male who was admitted to The Mount Sinai Hospital with a history of recurring episodes of unsteady gait, double vision, and oscillopsia. On examination, the gross fields of vision were within normal limits for movement. There were bilateral relative central scotomata, more marked on the left. There was optic atrophy in O.S. and optic pallor in O.D. During funduscopy, there was a distinct retinal nystagmus with a vertical component in O.S. and horizontal component in O.D. There was monocular oscillopsia during optic fixation with either eye more prominent on the left. There was also the illusion of movement of a fixed target at a distance during binocular fixation while the head was turned from side to side or up and down. Laboratory data were unrevealing. Spinal fluid protein was 23 mg ml and there were 200 white cells per mm^3. He was treated with intrathecal Depo-Medrol, 40 mg on six separate occasions, with subsequent improvement of gait and coordination.

Case #2: (R.A.)

In August 1973, this 35-year-old female noticed, while driving, that vision of the left eye seemed foggy and had to drive with the left eye partly closed or squinting. In August 1975, while driving at night, she noted that she saw two sets of tail lights, one above the other. As time progressed, the initially intermittent symptoms became constant. On November 1975, while lying in bed, she observed that everything was moving rapidly up and down. In the fall of that year, she lost hearing in the left ear but continued to have a tremendous noise, "like the sound of a drill," in the left ear.

The findings were related to her oculomotor system; there was intermittent eyelid retraction, the gross fields of vision were within normal limits and there were no scotomata. There was distinct oscillopsia in the horizontal plane in the left eye. The fundi were unremarkable, but during fundoscopy, the retina in the left eye was moving around from side to side and had a rotary component. There was minimal but distinct rotary retinal nystagmus, also in the right eye. There was incessant eye movement on fixating a target directly in front of her. Optokinetic nystagmus could be induced in all meridians but the response was irregular. Placed on Cortisone, she was again able to read and drive. When Cortisone was tapered, her balance became worse.

She was reexamined and an EOG was performed on May 17, 1976. At that time, looking straight ahead she could easily see the examiner; his image, however, appeared to be moving. Closing one eye made the image move much more. When looking at distant objects, they seemed to jump; but this was not the case when objects were close to her. On closing both eyes, the image disappeared.

On examination, the left eye was continuously moving, but not the right. There was opsoclonus of O.S. on conjugate horizontal gaze with a rotatory component. Actually, it seemed at times different with one horizontal and rotatory and one indepth component. The patient placed a glass on the table and drew a picture of what she saw in an attempt to describe the image. Figure 1 illustrates her own drawing of the moving glass as well as that of a candle. When questioned in 1977 and again in 1978, the patient reported that her eyes jumped less than three years before but that "they were never still." She was able to read but had not found any device to stop or decrease the eye movements.

Case #3: (B.P.)

In mid-December 1975, this 82-year-old patient had pain over the right eye. The pain extended toward the bridge of the nose and across to the left eye. During this time, he also became aware of diplopia in the horizontal plane. He also had difficulty in reading and a somewhat unsteady gait with a tendency to veer to the right. On neurologic examination performed one month later, the only significant findings were in the visual examination. During horizontal eye movements, especially to the right, there was lagging adduction, in O.S. along with horizontal, irregular nystagmus in the right eye. With the red glass test, there was crossed diplopia at both distant and near point and more on right lateral gaze than on left lateral gaze. Convergence was present. Upward and downward eye movements were normal. During fundoscopy, there were distinct irregular movements, side to side and, at times, rotary of the optic disc. In other words, there was "retinal nystagmus" in the right and, to a lesser degree, in the left eye. There was no oscillopsia. The patient reported that when reading a newspaper, the vision was usually clear but at times it was not. He observed that when he covered either eye, he could read better. The visual acuity was 20/20 on the Snellen Chart in both eyes. The visual fields were equal and the pupils reacted to light. The remainder of the neurologic examination was normal. About February 7, 1976, the patient noticed difficulties in walking and a few days later, his vision became worse and diplopia increased. During the ensuing six weeks, he had difficulty reading a newspaper and trouble in writing. On examination, the Romberg was positive and he veered to the left and backwards. The gait was broad-based, short-stepped and unsteady and, at times, he had to hold on for support. The finger-to-nose tests and power in both upper extremities were excellent. There was distinct bilateral heel-to-knee dystaxia. All deep tendon

TABLE I

Characteristics of Opsoclonus and Oscillopsia

1. The eye globe can be seen moving rapidly with the naked eye. If the eye appears still, the retina appears moving.
2. The oscillating eye movements are always present.
3. The eye movements are rapid, 4–5 per second, and of varying amplitude and direction.
4. The eye movement may vary between eyes.
5. Rarely, only one eye appears to oscillate.
6. After closing the eyes or in darkness, the eye movement continues but the oscillopsia disappears.
7. Head and body movement usually increase oscillopsia
8. Visual acuity is always affected.
9. Oscillopsia is usually more marked at distance.

reflexes were present. The left ankle jerk was depressed. There was no Babinsky sign. Vibration, position and pin-prick sensibilities were normal.

The gross fields of vision were normal. The visual acuity without glasses was 20/70. Both eyes were oscillating at a very rapid rate, mostly in the vertical plane. It was difficult to determine whether the jerking was upward or downward, but it was irregular, unequal, and more prominent in the right eye. During fundoscopy, the irregular movements were again apparent–these were either rotatory, vertical, or horizontal. The rate and amplitude of retinal nystagmus were rapid, variable and the movements were unequal and greater in the right eye. The pupils were equal and reacted to light. The jaw, face, palate, and tongue movements were normal. Mentally, the patient was perfectly clear.

The EOG performed February 1976 and repeated May 1976 (Fig. 2) illustrated the incessant eye movements. Biopsy of one of many lymph nodes appearing six months after his disease onset was consistent with lymphoma. The patient deteriorated gradually and died in a nursing home. No autopsy was obtained.

Case #4: (A.B.)

In 1955, this 52-year-old female reportedly had neuritis of the right eye. In 1960, she noted that vision in the left eye tended to "jiggle"; this was constant. She was well until May 11, 1976 when she noticed a sensation of numbness in the ball of each foot. This numbness spread upward to the waistline and the lower portion of the thoracic cage. On May 15, 1976, the numbness extended further involving the left arm, the outer three fingers of the hand, and part of the forearm above the elbow. On examination, the gross fields of vision were within normal limits, but she had difficulty seeing many of the pseudosochromatic plates with either eye, especially the left. She made some errors in the left temporal field. Visual acuity in the right eye was 20/30 and in the left, 20/50. The optic papilla in the left eye showed some pallor on the temporal side. There was questionable pallor in the right eye. She had rapidly oscillating eye movements bilaterally on forward gaze, sometimes moving in different directions and less prominent in the right eye. Marked retinal nystagmus could be observed during fundoscopy. Rapid oscillating eye movements with mixed horizontal and vertical beats occurred when the eyes turned in any of the four cardinal gaze directions. She had crossed diplopia at near point with the red glass test. Optokinetic nystagmus could be easily induced and was superimposed on the resting nystagmus in both eyes. The spinal tap was unremarkable except for protein of 55 mg %. She received 40 mg of Depo-Medrol intrathecally on two occasions with improvement in vision and ambulation. This was followed by oral Prednisone, 20 mg bid. When requestioned in 1977, she still had oscillopsia. When closing the left eye, objects "jumped less" and she could read better. However, for prolonged reading, the patient used both eyes. Varying the object distance from the eyes did not improve the vision, but the oscillopsia seemed more pronounced at distance. Closing the eye caused the oscillopsia to disappear–moving the head or the body did not change the characteristic of oscillopsia.

Discussion

Exacting an accurate description of symptoms and a simple inspection of eye movements will provide the diagnosis of oscillopsia. Although a careful history will be suggestive of oscillopsia, on rare occasions, the eyes will not be seen jerking even when examined under Frenzel lenses (2). In these instances, fundoscopy will provide the clue; rapid to and fro, small amplitude movements of the retina "retinal nystagmus" will be noted. How movements of the posterior pole coexist without visible movement of the ocular globe is not understood.

Oscillopsia was a prominent and disturbing feature during the first few weeks of disease in all patients presenting with disorders of brain stem and cerebellum. To our knowledge, however, Case #3 is the first adult presenting opsoclonus and oscillopsia associated with lymphoma of the CNS. A sample electrooculography (EOG) and its changes over time are shown in Figures 2 and 3. Although the patient developed a head tremor three months later, he could read big print letters, a task he could not perform previously. Surprisingly, a sample of his EOG revealed worsening of his eye movement (Fig. 3). The EOG showed large amplitude vertical bursts up to 50 degrees. These occurred infrequently and were superimposed on smaller amplitude continuous movements of 4 to 5 cycles per second. Occasionally, rotatory components, which the EOG cannot record, were seen by the examiner. At times, the main eye movement vector was horizontal, changing a few seconds later to become vertical. Eye closure or darkness had little effect on the eye movements since the patient reported on definite sensation of continuous eye movement. Upon examination of their eyes, all the patients displayed rapid, irregular eye movement of different amplitude, speed, and direction. The movement characteristic of one eye was usually different from the fellow eye. In two patients with amplitude and speed variations between fellow eyes, the closure of the "eye jumping more" decreased oscillopsia. In those cases, gaze with one eye was favored for close scrutiny (Cases #2, #3).

The direction of imagined movement in oscillopsia depends upon the direction of the eye movement. Thus, it will be vertical if the oscillopsia is vertical, horizontal if the eye moves horizontally, etc. Actually, the eye vector is rarely pure horizontal or vertical, often having an oblique component. Moreover, Patient #2, as well as a patient reported by Bender (1,2), had what appeared to be a movement indepth, as if the eye globe was "sucked in." The resultant image is both disturbing and confusing to the patient. The association of oscillopsia with various types of field defects or decreased acuity, as seen in MS (Case #1), will render vision that much worse. Most often however, visual acuity is imparied because of the oscillation of the images.

If the visual acuity decreases progressively, an ongoing disease must be ruled out since in MS, the characteristics of oscillopsia fluctuate minimally over the years (Case #2 and #4). One patient (Case #4) reported that alcohol "made things jump more." The use of sedatives did not change the characteristics of oscillopsia. The eye movements reportedly are decreased during sleep (19). The effects of anesthesia are not known.

The oscillopsia of our patients has never ceased over the years (up to 18 years in Case #4), and the patients always were aware of its presence. Fluctuation in intensity may occur at times, especially in the morning after having rested when the oscillopsia may decrease (Case #1). Patients #1 and #4 seem to have adjusted to their visual disability, using both eyes for prolonged reading or for watching television. They deny visual fatigue. Most of the patients do not drive a car, but this may be related to the presence of other disabling effects of MS. Patients were asked if moving the head or body, or if walking influenced the oscillopsia. Cases #8, #9, #10, and #11 of Bender, and our Case #2 reported worsening of the oscillopsia upon moving the head and body. Patients with bilateral eighth nerve disease or labyrinthine disorder will report marked worsening of oscillopsia if the labyrinth is stimulated directly (caloric testing), or if the head is turned passively (20,21). Depending upon the speed of eye movement, the image and the background will appear to be oscillating at various frequency in space. A patient with continuous, slow velocity (one movement per second) eye movements recently confirmed that a certain speed of eye movement is necessary for oscillopsia to appear; this patient had always denied oscillopsia or blurring of vision (personal case).

The clinical presentation and course of this syndrome are consistent mostly with lesions of the cerebellum and the brain stem. The few cases in which pathology was available had lesions of the brain stem, cerebellum and, less so, in the hypothalamus (7, 9). In carefully studied cases, lymphocytic infiltration around vessel areas in the brain stem are reported (7). Some investigators underscore this feature and attribute the etiology of this syndrome to an allergic inflammatory process (11, 12). Good results with the use of steroids favor such a hypothesis. Oscillopsia is not always reported with opsoclonus. One likely reason is that patients are not questioned carefully or are too sick. Furthermore, the neuroblastoma cases occurring in young children preclude an accurate history.

Oscillopsia and, concomitantly, visual acuity improved in all cases treated with steroids. Improvement consisted of a decrease in the amplitude of an object's apparent movement and in the ability to "focus on images." Such an improvement enabled Patient #2 to read and to drive again.

Acknowledgments

Thanks are extended to Dr. M. B. Bender for kindly allowing me to examine and follow these patients. Thanks, too, to Mrs. Magdalena del Rojario for her technical assistance.

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Cytomegalovirus Inclusion Body Endocervicitis: Significance of CMV Inclusions in Endocervical Biopsies

Ludwig M. Deppisch, M.D.

Abstract

Viral inclusions are infrequently detected in cytomegalovirus (CMV) endocervicitis. This report of a seventh case illustrates the pathologic and clinical features of CMV inclusion body endocervicitis. A marked inflammatory process, characteristic but nondiagnostic, marks the histopathologic appearance, but morphologic diagnosis is based upon detection of the characteristic inclusion bodies. Clinical manifestations vary from absent or nondescript findings to extensive cervical erosion. A series of biopsies in culturally positive women will be required to completely elucidate the microscopic and clinical appearance of CMV endocervicitis.

CMV inclusion body endocervicitis may reflect either systemic or localized disease, more commonly the latter. Venereal transmission may be one mechanism that initiates localized disease. Although neonates may be infected during interpartum passage through an infected cervix, significant infant disease apparently does not result.

Introduction

Cytomegalovirus (CMV) inclusions have very rarely been noted in endocervical biopsy sections. However, CMV infection of the endocervix is not a rare event, since this virus has been recovered from cervical cultures in 3-14 percent of patients (1-3). The clinical consequences of CMV endocervicitis are not entirely clear, particularly the possibility of perinatal transmission of CMV in the pregnant female.

The unanticipated presence of CMV inclusions in an endocervical biopsy prompted the following case report and literature review. The pathologic, clinical and obstetrical consequences of such a finding will be discussed.

Case Report

A 15-year-old, nulligravid female was admitted with the complaint of menometrorrhagia and with multiple condylomata accuminata of the labia majora and minora. Examination of the cervix disclosed an extensive circumoral, circumferential, friable hemorrhagic erosion. The condylomata were limited to the vulva. The admission white blood cell count was 7,900/mm^3 with 51 segmented pmns, 13 bands, 34 lymphocytes and 2 monocytes. The VDRL was nonreactive.

The condylomata were fulgurated and a uterine dilatation and curettage, and cervical biopsy were performed.

Microscopic sections disclosed characteristic intranuclear and intracytoplasmic CMV inclusions within occasional columnar epithelial cells lining endocervical glands (Fig. 1). The infected cells were mostly in the mid-zone or base of the gland (Fig. 2). Occasionally, CMV inclusions were noted in several cells within the same gland; many of the infected cells protruded into the glandular lumen (Fig. 1). A prominent, diffuse, nonspecific inflammatory infiltrate composed of neutrophils, lymphocytes and plasma cells was noted (Fig. 2). A few nodular lymphoplasmacytic aggregates were present but discrete lymphoid follicles were not observed (Fig. 3). Microulcerations of surface

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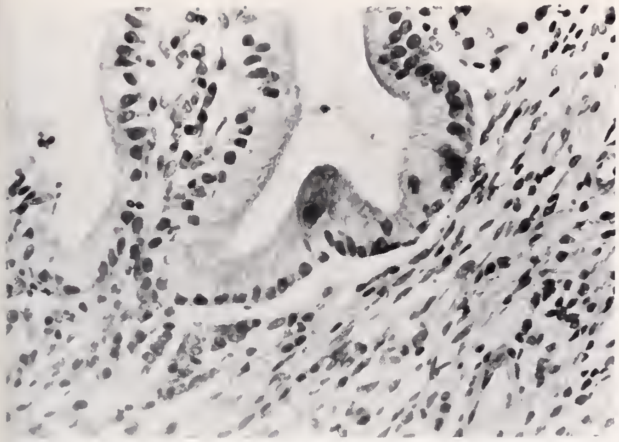

FIG. 1. CMV intranuclear and intracytoplasmic inclusions within endocervical cells, in process of extrusion into lumen. (H & E × 500).

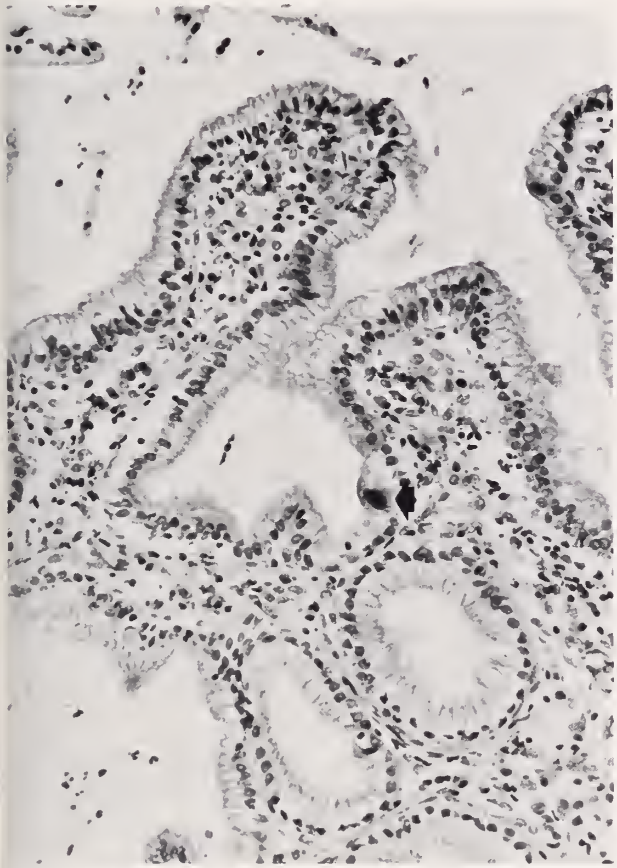

FIG. 2. CMV infected endocervical cell situated in midzone of gland (arrow). Marked stromal exudate consisting of neutrophils, plasma cells and lymphocytes. (H & E × 325).

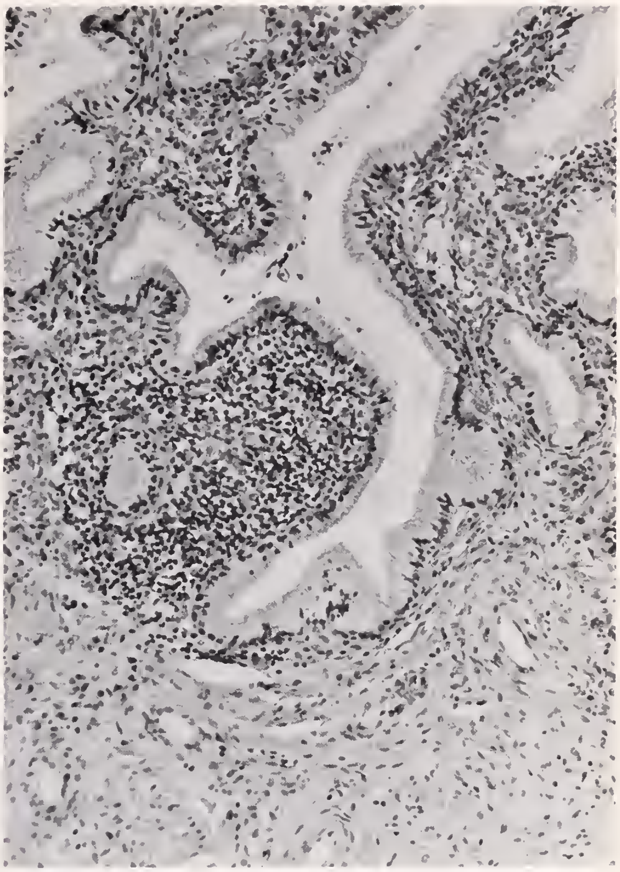

FIG. 3. Stromal lymphoplasmacytic nodule, unassociated with CMV inclusions (H & E × 170).

endocervical epithelium and focal gland necrosis were also noted. None of these changes were particularly related to the cells containing CMV inclusions. The exocervix was unremarkable. The endometrium was in late secretory phase, and neither epithelial nor stromal cells contained CMV inclusions.

Antibodies to CMV were detected in the patient's serum, using indirect fluorescent techniques, at a titer of 1:16 at one and five weeks after biopsy. However, CF antibody titers were not demonstrated in the patient's acute or convalescent sera. The urine was negative for CMV, both by culture and cytologic examination.

Discussion

CMV infection of the endocervix is uncommon, but not rare in the United States. Positive endocervical cultures have been obtained in as many as 14 percent of women in selected populations (1). A positive correlation has been established for pregnancy, a younger age group, and lower socioeconomic status (1–3, 7).

Despite this, morphologic hallmarks of CMV infection, the characteristic intranuclear and intracytoplasmic inclusions, have been described in endocervical biopsies only six times previously (4–6). Autopsy series have also documented that the endocervix is an extremely rare site for CMV inclusions (8, 9).

In a recent autopsy series, Smith (10) has shown that this virus is detected in infected organs much more frequently by culture than by morphologic means. Since it is unlikely that the characteristic CMV inclusions have been overlooked repeatedly upon pathologic examination, the exaggerated cultural morphologic discrepancy could be attributed either to sampling error or, more likely, to the lack of reliability of inclusion bodies as a marker of virus infection. The presence of CMV inclusions in the endocervix indicates a signficant infection, and has been associated with a marked, inflammatory reaction in all the reported cases.

Wenckebach and Curry (4) assert that this inflammatory reaction, although nondiagnostic, is characteristic and includes a prominent lymphoplasmacytic infiltrate, lymphoid follicles with germinal centers, and anatomic evidence of a rapid turnover of endocervical epithelial cells. The present case displays all of these features with the exception of discrete lymphoid follicles. Infected epithelial cells were detected in the process of exfoliation into endocervical gland lumina, a sign of increased cellular turnover that may result in viral shedding.

However, cervical biopsies have not been performed upon culturally positive patients in high risk groups to assess the histopathology of the cervical infection in a series of cases.

Since the morphologic changes described above can be noted in a variety of cervical infections, the morphologic diagnosis of CMV endocervicitis most certainly rests upon the detection of the specific intranuclear and intracytoplasmic inclusions. These inclusions reside more frequently within the columnar epithelium of endocervical glands (4–5). However, in two patients, endothelial cells and fibroblasts were also infected. It is interesting that both patients exhibited systemic disease, one with CMV mononucleosis (4) and the second with fatal systemic congenital CMV infection (11).

The clinical manifestations of endocervicitis with demonstrable CMV inclusions have not been uniform. In two instances, including the present case, extensive cervical erosions prompted biopsy (5). In a third case, only a Schiller nonstaining area of the cervix was observed in a patient with vaginal discharge (6). In the remaining cases, the clinical manifestations were either absent or unreported (4).

It is probable that CMV endocervicitis may represent either systemic or localized disease. In several cases (4, 11) endocervical CMV inclusions have been observed in active systemic disease.

In the majority of culturally or morphologically proven cases, extracervical disease is not apparent, although its presence has not always been thoroughly investigated. Urine cultures are frequently negative in patients with positive endocervical cultures (3).

There is an increased incidence of positive endocervical cultures in pregnant women, as well as increasing incidence of positive cultures with length of pregnancy. This has been offered as evidence that endocervical infection represents local reactivation of a previously systemic, but latent infection (3).

However, at least some cases may be venereally transmitted. There is a positive correlation between the incidence of positive cultures and the occurence of gonorrhea, and CMV has also been recovered from semen (1). The presence of large numbers of condylomata accuminata, and the absence of pregnancy, in our case, may offer circumstantial support for a venereal mode of transmission.

The limited number of reported cases and the absence of meaningful follow-up provide no information regarding neonatal or perinatal viral transmission in CMV inclusion body endocervicitis. However, it is known that a significant number of infants of mothers with culturally positive CMV endocervicitis, will develop a CMV infection during the first few months of extra-uterine life. This infection is probably acquired during perinatal passage through an infected cervical canal. These infants are usually asymptomatic and the great majority appear to develop normally with no long term deleterious effects (1, 7).

The severe neurologic problems of congenital CMV disease have not been attributed to CMV endocervicitis (3). Congenital infection has been associated with a primary maternal infection during pregnancy (2), in which hematogenous and transplacental transmission produces fetal disease. Congenital CMV disease is acquired in utero, rather than during perinatal passage through an infected cervix. Therefore, it seems probable, that unlike Herpes infection of the cervix, the detection of CMV endocervical inclusion bodies, does not bode ill for concurrent or subsequent offspring.

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The Value of Cholangiogram in Common Bile Duct Exploration

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Unseen stones in the common bile duct are a constant cause of anxiety for the surgeon performing a cholecystectomy for calculous disease of the biliary tract. Retained stones are not only a source of embarrassment to surgeons, but more importantly constitute a source of significant morbidity and mortality to patients. The desire to prevent this problem is well reflected in the conventional indications for exploring the bile duct at the time of cholecystectomy. These encompass a wide spectrum such as: palpable stones in the bile duct, the presence or history of jaundice, dilatation of the common bile duct, history of pancreatitis, and small stones in the gallbladder. To this end, many surgeons perform operative cholangiograms to visualize the biliary system prior to exploration of the bile duct. In an attempt to minimize the incidence of overlooked stones in the common bile duct, and to minimize unnecessary common bile duct exploration, we have established a general policy that an operative cholangiogram should be performed in every patient who undergoes cholecystectomy, unless the patient has already had the bile duct visualized adequately by intravenous, transhepatic, or endoscopic retrograde cholangiogram preoperatively.

This study was undertaken to analyze our own experience and to evaluate the reliability of roentgenologic studies in determining whether common bile duct exploration should be done at the time of cholecystectomy.

Materials and Methods

The medical records were reviewed of 230 patients who underwent cholecystectomy in the Department of Surgery, City Hospital Center at Elmhurst, a major affiliate of Mount Sinai School of Medicine of The City University of New York, during the period January 1974 to December 1977. Excluded from the review were patients who underwent cholecystectomy as a secondary procedure, or who underwent secondary common bile duct exploration, and patients who were found to have noncalculous diseases of the biliary tract, such as malignant tumors of the gallbladder, bile duct, sclerosing cholangitis, or biliary obstruction secondary to chronic pancreatitis. All patients were managed by surgical residents under the close supervision of attending surgeons. One of the authors (U.K.) was involved in the decision making process in practically every patient, thus maintaining some uniformity in patient management.

Analyses were made of the age of the patients, their sex, laboratory findings, findings of cholangiogram, indications for common bile duct exploration, incidence of finding stones in the common bile duct, retained stones, and postoperative complications and operative mortality. An operative cholangiogram was obtained by injecting approximately 6.0 cc of 25% solution of Diatrizoate Sodium (Hypaque Sodium) into the common bile duct through a catheter placed into the cystic duct stump. A second study was performed by injecting about 3.0 cc of the dye a few minutes later to allow the dye to enter the duodenum. When the cystic duct cannulation was found difficult, the common bile duct was directly punctured with a 22 guage needle and cholangiogram was performed. When the cholangiogram was of technically suboptimal quality or showed air bubbles, the

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study was repeated until a good quality cholangiogram was obtained. Tilting the operating table so that the common bile duct was shifted away from the underlying spine, changing the concentration and/or amount of contrast medium according to the size of the bile duct were maneuvers often used to improve the quality of the cholangiogram. Following exploration of the duct, and around the tenth postoperative day, T-tube cholangiogram was repeated before its removal.

Results

Age and Sex: There were 56 males and 174 females. Sixteen males and 40 females underwent common bile duct exploration. The ages of the patients ranged from 18 to 92 years. There were more elderly patients in the common bile duct exploration group as compared to the cholecystectomy alone group (Table I).

Operative Cholangiogram: Operative cholangiograms were obtained in 172 out of 230 patients (75%), 41 out of 56 who underwent common bile duct exploration, and 131 out of 174 patients who underwent cholecystectomy alone. The reasons for not performing operative cholangiograms were essentially preoperative cholangiograms that had visualized the ductal system adequately, and the presence of palpable stones in the common bile duct, as illustrated in Table II.

Common Bile Duct Exploration: Fifty-six patients underwent common bile duct explorations. In 46 patients, stones were removed, with a positive common duct exploration rate of 82.1% (Table III).

When Preoperative or Operative Cholangiograms Demonstrated Stones or Findings Highly Suspicious of Stones.

Of the 45 patients in this group, stones were removed from the bile duct in 37 patients (82%). No stones were found in eight patients.

TABLE I
Age and Sex

	CBD		Cholecystectomy Alone	
Age	M	F	M	F
10-29	1	7	0	35
30-49	1	11	12	49
50-69	6	11	19	36
70+	8	11	9	14
Total	16	40	40	134

TABLE II
Reasons For Not Doing Cholangiogram

	CBD Group	Cholecystectomy Alone Group
1. IVC or THC or ERCP visualizing the duct	4	13
2. Palpable stones	5	0
3. Dilated duct	4	0
4. Pancreatitis	2	0
5. Technical difficulty, no clinical findings for CBD stone	0	30
Total	15	43

TABLE III
Positive CBD Exploration

	Number of Patients	Stones Found	Percent
1. Positive Cholangiogram preoperative or operative	45	37	82%
2. Palpable stone	5	5	100%
3. Jaundice	55	33	60%

When Stones were Palpated in the Duct

All five patients had stones removed from the duct.

Jaundice

Fifty-five patients had serum bilirubin over 2.0 mg.% on admission. Cholangiogram showed evidence of stones in the bile duct in only 41 patients, who underwent common bile duct exploration. Stones were removed from the bile duct in 33 patients (80%). Therefore, the incidence of common bile duct stones in the jaundiced patients was 60%. There was no correlation between the level of serum bilirubin and the incidence of the common bile duct stones.

Retained Stones: Postoperative cholangiogram showed evidence of retained stones in two patients. Attempts at removal of the stones with the use of the Dormia basket were unsuccessful in one patient, and the stones were subsequently removed operatively. In the other patient, the stones were flushed out successfully with infusion of Heparin-saline solution into the bile duct through the T-tube.

Complications: Eight patients developed postoperative complications; three pulmonary complications, two wound infections, one postoperative pancreatic abscess, which required surgical drainage with an uneventful recovery, and two transient renal failure cases with full recovery.

Mortality: Three patients died, with a mortality of 5.3% among the 56 patients who underwent common bile duct exploration. There were no deaths among the cholecystectomy alone group. The mortality of the entire series therefore was 1.3%.

A 78-year-old male with advanced arteriosclerotic heart disease underwent an emergency cholecystectomy and common bile duct exploration for an acute gangrenous cholecystitis and choledocholithiasis. The postoperative course was complicated by acute renal failure, which was treated with peritoneal dialysis. The patient expired approximately one and one half months after the operation, following an acute onset of tachypnea and pulmonary edema. The autopsy showed bilateral bronchopneumonia and a massive pulmonary embolism.

A 63-year-old male was admitted with clinical pictures of acute cholangitis. He underwent an emergency cholecystectomy, and a cystic cholangiogram showed a stone impacted in the distal bile duct. Attempt at the removal of the stone through a choledochotomy was unsuccessful, and a duodenotomy was performed. Even through the duodenotomy, however, the stone could not be dislodged. The procedure was terminated with insertion of a T-tube into the common bile duct, and the duodenum was closed. Postoperative course was complicated by leakage of the duodenotomy site, which persisted. The patient subsequently was re-explored, primarily to divert the duodenal fistula by performing a vagotomy and gastrojejunostomy. He developed severe bronchopneumonia with sepsis and expired.

An 86-year-old woman was admitted with clinical pictures of acute cholangitis. After her septic picture abated, an intravenous cholangiogram showed multiple stones in the gallbladder, and a stone in the common bile duct. During the surgery, the patient developed an episode of severe hypertension, followed by cardiac arrest. She was resuscitated, but never regained consciousness and subsequently died.

Discussion

Despite substantial experience that a surgeon may have in the operative management of the biliary tract disease, the decision to explore the common bile duct at the time of cholecystectomy is not always easy to make. While the conventional indications for common bile duct exploration are generally reliable, relying on these alone may result in errors of both commission and omission.

Palpable stones, acute cholangitis, and preoperative demonstration of stones in the bile duct are absolute indications to explore the duct, whereas jaundice, dilatation of the common duct, pancreatitis, and small stones in the gallbladder are relative indications. When faced with these latter relative findings, operative cholangiography can provide important information regarding the stones in the bile duct. Operative cholangiogram as a means of demonstrating the pathology of the bile duct at the time of cholecystectomy has gained wide acceptance because of its simplicity and objectivity. Yet, its routine use has not been universally accepted. The common arguments against its routine use are: 1) it prolongs operating time, 2) it can be misleading, and 3) it is not necessary when there are no clinical or operative findings to indicate the presence of stones in the common duct.

Our study, however, showed that carefully performed, properly interpreted cholangiograms helped in obtaining a high rate of positive common duct exploration (82%), and in avoiding unnecessary exploration of the common duct in 14 jaundiced patients. This figure is somewhat better than other positive common bile duct exploration rates for stones: 63% by Jolly and associates (1), 65% by Way and coauthors (2), all of whom use operative cholangiograms frequently, but not always. In contrast, Bartlett and associates (3) reported positive common bile duct exploration rates for stones to be 38%, Calcock and Perry (4) reported it to be 27.6%, Shoefield and associates (5) reported it to be 54%, and Glenn (6) reported it to be 61.1%. These latter authors did not use cholangiograms frequently.

It cannot be overstressed that to use the cholangiogram as a reliable source of information, it is essential that a good quality cholangiogram is produced. This requires not only the experience and patience of the operating surgeon, but also the cooperation of the anesthetist and x-ray technician. As cautioned by Hall and his associates (7), misinterpretation, inadequate visualization of hepatic radicles and distal end of the common bile duct, particularly following the manipulation of the ampullary region during the common bile duct exploration, are potential sources of problems. It is common to find that the contrast medium does not flow into the duodenum in T-tube cholangiogram immediately following the exploration of the bile duct due to spasm of the ampulla of Vater, making correct interpretation of the cholangiogram difficult. This can be overcome by obtaining the operative cholangiogram prior to exploring the bile duct even when stones are palpated in the bile duct.

To overcome many difficulties encountered during the exploration of the bile duct, some surgeons are using choledochoscopy to examine the lumen of the duct under direct vision. The choledochoscopy, particularly with flexible choledochoscope, seems to offer the potential of complimenting the cholangiography.

Our study confirms the general observation that choledocholithiasis is more common among the elderly patients. With higher surgical risks among this group of patients, surgeons are obligated not to overlook stones in the bile duct, and yet not to explore the duct unnecessarily by careful examination of the bile duct with cholangiogram.

We conclude that although the convential indications for common duct exploration are useful, routine operative cholangiogram has provided us most essential information regarding the stones and other pathology in the bile duct. It does not prolong the operating time unduly; it helps to lessen the chances of overlooking stones in the bile duct, and also minimizes unnecessary exploration of the bile duct. We, therefore, recommend that operative cholangiogram be performed in every patient prior to exploring the duct, unless the stones are palpable in the bile duct or the biliary duct has been well visualized preoperatively regardless of the presence or absence of the conventional indications for exploration.

Summary

The use of routine operative cholangiogram prior to exploration of the bile duct at the time of cholecystectomy in 230 patients was evaluated. The study indicates that carefully performed and properly interpreted cholangiograms have been significant factors in obtaining a high rate of positive common bile duct exploration. We recommend that operative cholangiogram be performed at the time of cholecystectomy, unless the bile duct has been well visualized preoperatively, to minimize the chance of overlooking the stones.

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The Hyaline Eccrinoma

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The histogenesis of the so-called cylindroma is still uncertain. Sites of origin favored include apocrine structures (1, 2), the pilary complex (3), and eccrine structures (4). After meticulous histologic study of a number of these lesions, I must conclude that they originate from the eccrine gland.

Materials and Methods

Skin biopsies of six solitary lesions showing characteristic clinical and histologic features of so-called cylindromas were reviewed from the files of The Skin and Mucous Membrane Biopsy Laboratory. The series comprised two lesions each from the scalp, forehead and eyebrow. All patients were women ranging in age from 38 to 75 years. Staining techniques utilized included Hematoxylin and Eosin, periodic acid-Schiff with and without diastase and alcian blue (pH 4.5 and 0.5).

Results

All lesions showed similar microscopic features (Figs. 1–6). The epidermis was generally thinned and flattened with effacement of rete ridges. Except for a narrow band of uninvolved connective tissue within the subepidermal zone, most of the cutis and attached subcutaneous tissue were occupied by a benign epithelial neoplasm which tended to form a lobular pattern. The lobules were composed, for the most part, of uniform small epithelial cells arranged in compact anastomosing cords of various sizes and shapes surrounded generally by a conspicuous eosinophilic hyaline band of variable thickness and separated from one another by a narrow band of fibrous tissue. Each lobule was reminiscent of a mosaic of stone masonry. This hyaline band was PAS-positive, diastase-resistant. Hyaline material staining similarly was also identified in the form of apparent globules between the epithelial cells within many of these cords. The periphery of these cords was composed generally of a single layer of palisaded epithelial cells with ovoid hyperchromatic nu-

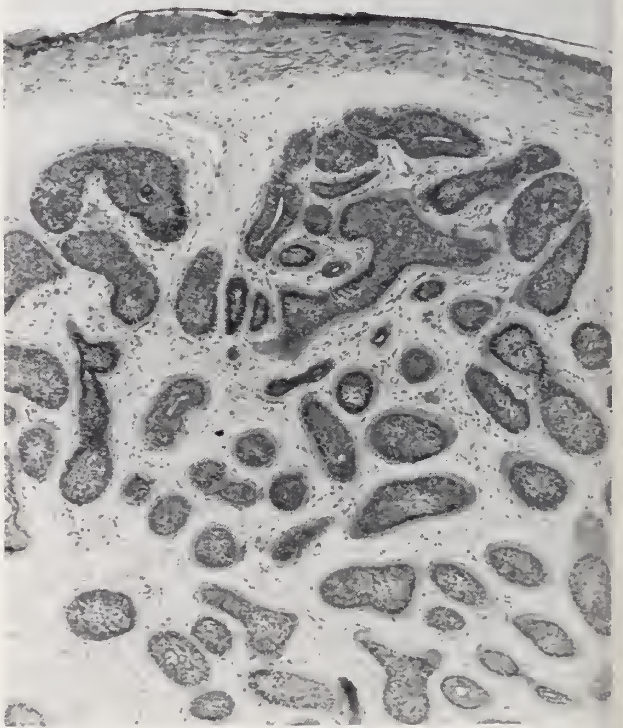

FIG. 1. Scanning view showing flattened epidermis, extensive involvement of cutis and subcutaneous tissue, characteristic compact nongeometric cords of epithelial cells assuming a lobular pattern, conspicuous hyaline sheaths about cords and stromal proliferation about lobules (H & E × 40).

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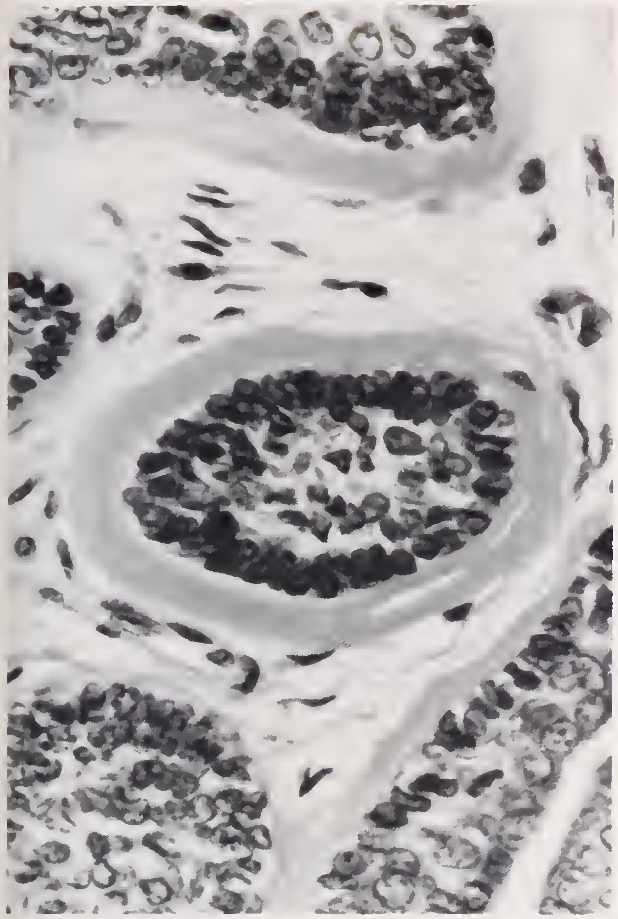

FIG. 2. High magnification detailing conspicuous hyaline sheath, peripheral layer of palisaded cells with hyperchromatic ovoid nuclei and cells with larger ovoid vesicular nuclei in center (H & E × 400).

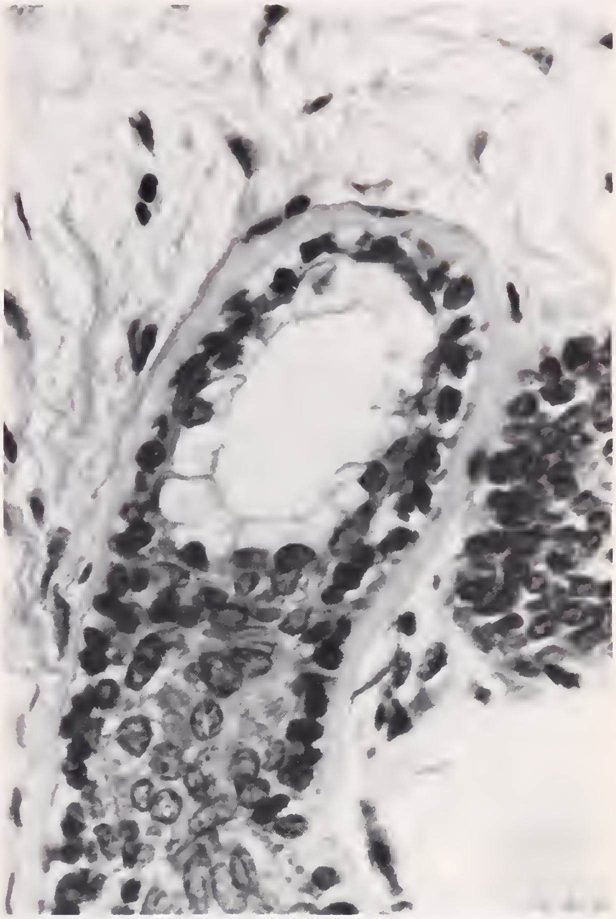

FIG. 3. High magnification demonstrating ductular structure lined by well-defined columnar and cuboidal cells with vacuolated cytoplasms (H & E × 400).

clei. The epithelial cells in the center had larger, ovoid nuclei with a vesicular chromatin network. The cytoplasms of both cell types were scanty, poorly defined and pale eosinophilic. Occasional mitoses were encountered within these epithelial cells.

Randomly distributed tubular structures of variable frequency were encountered within these epithelial cords. These tubular structures had a variable luminal layer of uniform epithelial cells. These cells assumed flat, cuboidal or columnar shapes. Their cytoplasms varied from scanty to abundant and densely eosinophilic and homogeneous to pale eosinophilic or basophilic with coarse or fine vacuoles. Cytoplasmic borders were either poorly defined or distinct. The nuclei were generally round and ranged from hyperchromatic to vesicular. PAS-positive, diastase-resistant granular and/or flocculent material was observed within the lumens of a number of these tubular structures. Small amounts of glycogen were identified within all epithelial cell types comprising the neoplasm. No acid mucopolysaccharide at either pH (4.5 or 0.5) could be demonstrated in the neoplasm with alcian blue.

Foci of stromal proliferation characterized by parallel bundles of loosely arranged collagen fibers and fibroblasts were observed about the lobules of epithelial cells in all cases. In one case, a few of the lobules showed the histologic features of an eccrine spiradenoma (Figs. 7, 8) characterized by compact interwining bands of uniform epithelial cells of both cell types similar to those described within most of the tumor.

Discussion

When one compares the histopathology of the so-called cylindroma to the normal histology of the eccrine gland (5, 6), one will note many similarities (Figs. 9-11). Both are arranged in compact coils. Both have tubular structures with PAS-positive, diastase-resistant luminal secretion; furthermore, the epithelial cells lining

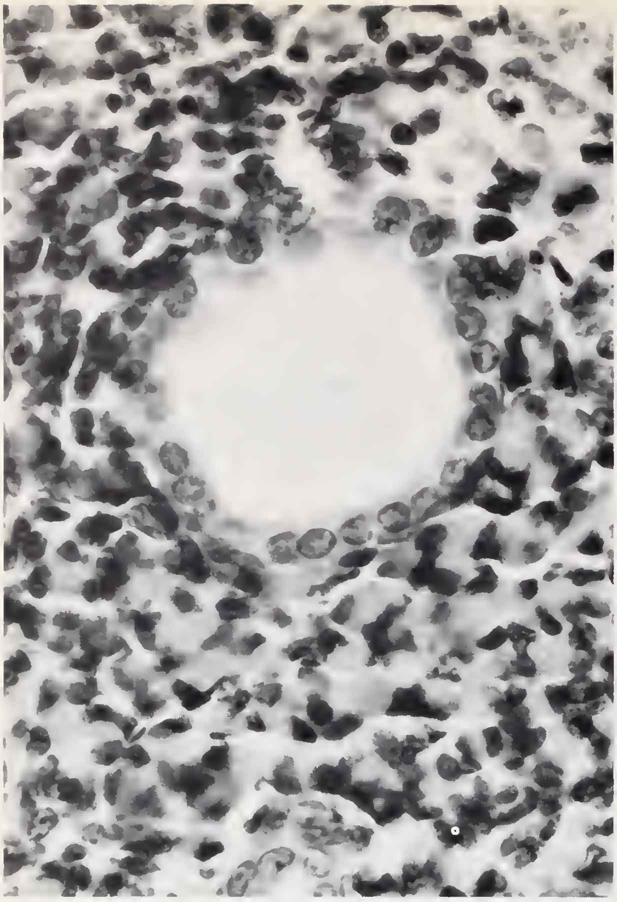

FIG. 4. High magnification showing ductular structure lined by poorly defined cuboidal and flat cells with scanty to moderate amount of homogeneous eosinophilic cytoplasms. Amorphous luminal secretion is present and hyaline droplets are conspicuous (H & E × 400).

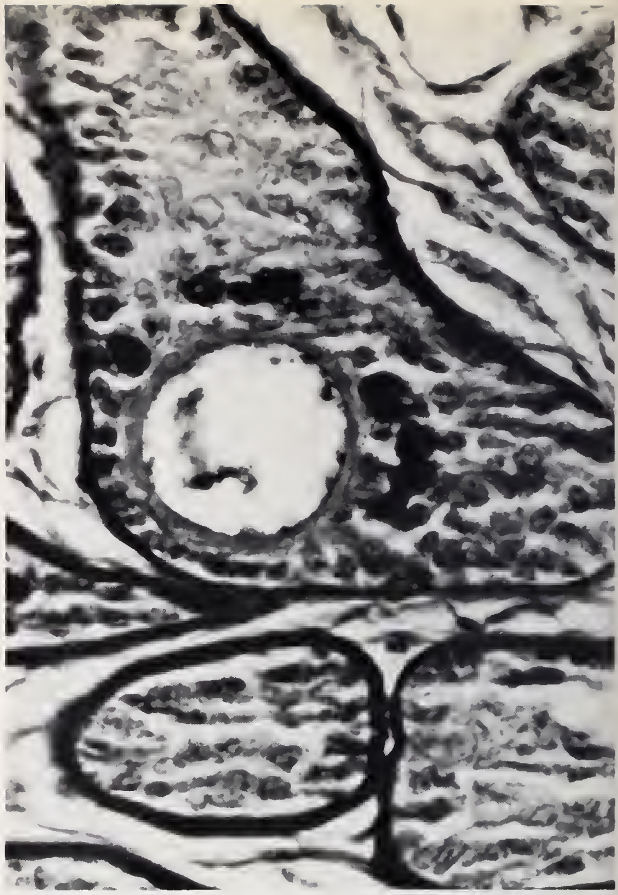

FIG. 6. High magnification showing PAS-positive, diastase-resistant hyaline droplets and material within lumen of ductular structure (PAS-diastase × 400).

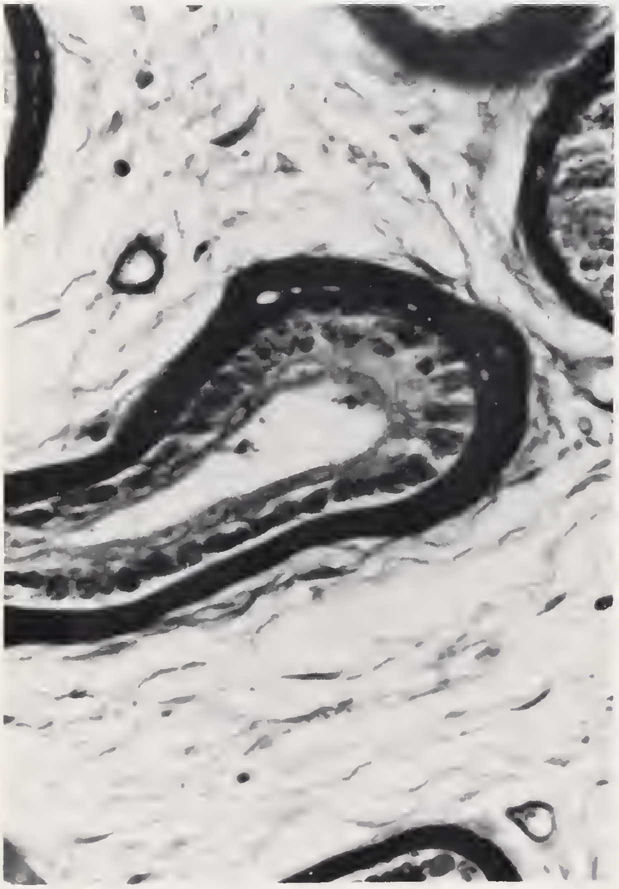

FIG. 5. High magnification showing conspicuous PAS-positive, diastase-resistant hyaline sheath (PAS-diastase × 400).

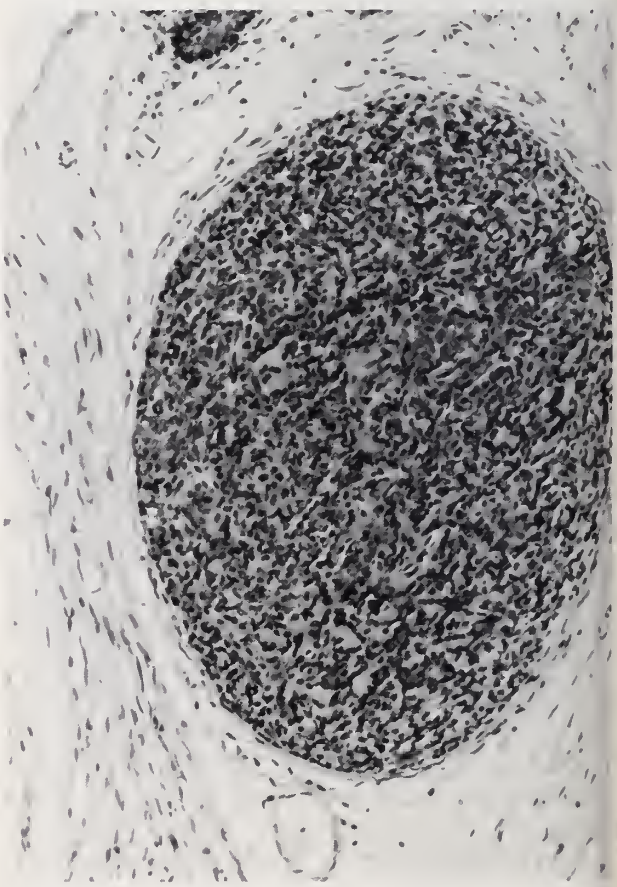

FIG. 7. Low magnification showing tumor lobule resembling eccrine spiradenoma. Note intertwining cords of small, uniform epithelial cells having either hyperchromatic or vesicular nuclei and absence of hyaline sheath (H & E × 100).

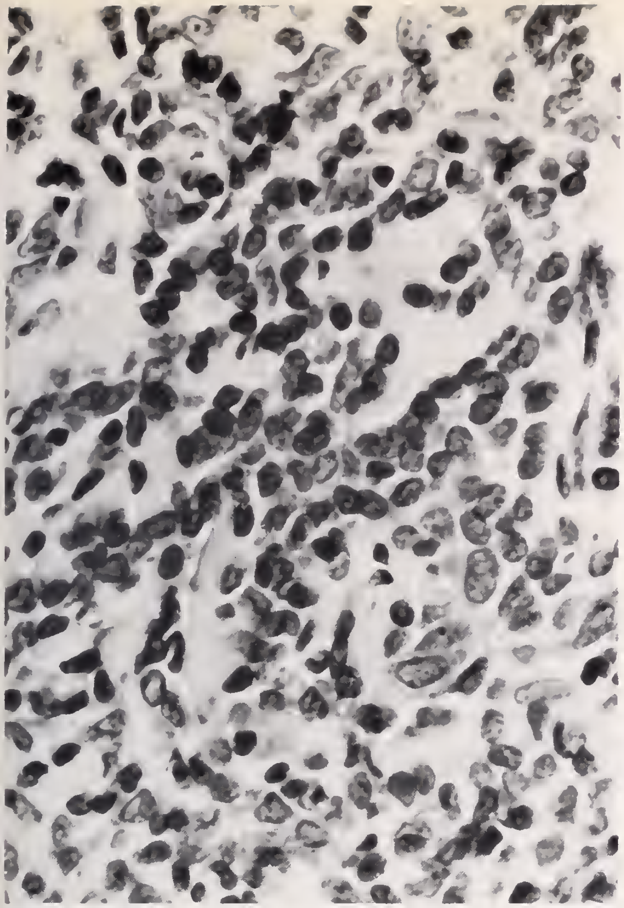

FIG. 8. High magnification of Fig. 7 detailing features (H & E × 400).

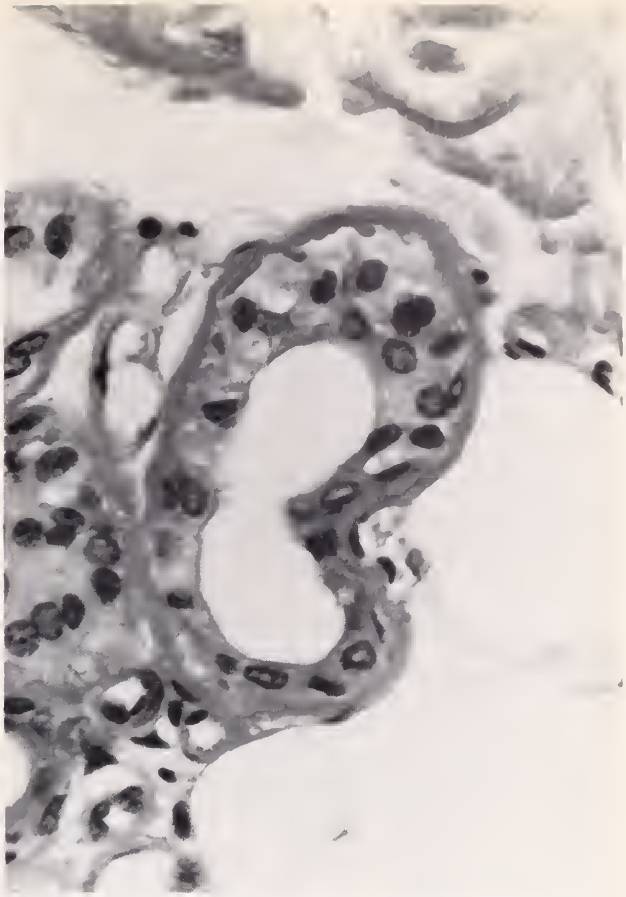

FIG. 10. High magnification of normal sweat gland showing prominent hyaline band in basement membrane zone and lining by poorly defined cuboidal and flat cells with moderate to scanty amounts of homogeneous cytoplasms. Note similarity to ductular structure in Fig. 4 (H & E × 400).

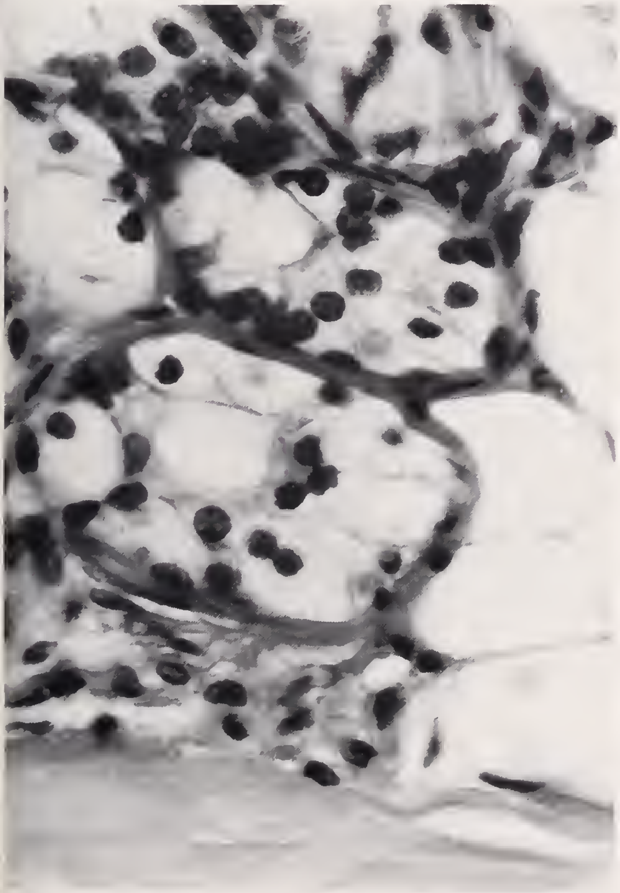

FIG. 9. High magnification of normal sweat gland showing prominent hyaline band in basement membrane zone and lining by well-defined columnar and cuboidal cells with vacuolated cytoplasms. Note similarity to ductular structure in Fig. 3 (H & E × 400).

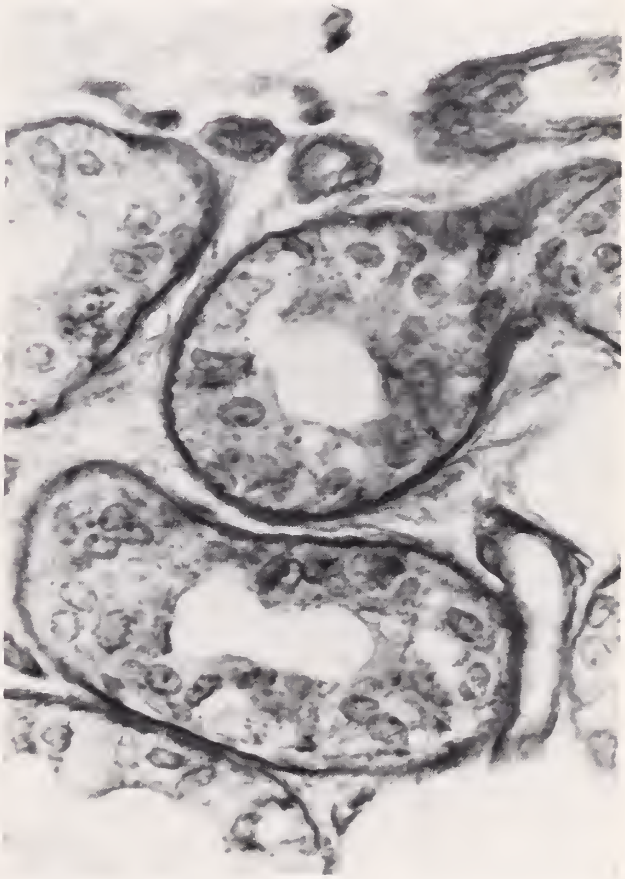

FIG. 11. High magnification of normal sweat gland demonstrating PAS-positive, diastase-resistant band in basement membrane zone (PAS-diastase × 400).

these tubular structures are similar to those observed in normal eccrine glands.

The eccrine gland has a conspicuous, eosinophilic, PAS-positive, diastase-resistant basement membrane zone like the hyaline band about the tumor cords. The peripheral layer of palisaded cells with oval hyperchromatic nuclei bears some resemblance to the myoepithelial cells about normal eccrine glands; both cells rest upon a prominent hyaline band or membrane and probably contribute to its formation; as suggested (1), the hyaline globules are probably secreted by the tumor cells and the hyaline sheath represents a combination of amorphous secretion by these cells and a fibrillary component secreted by fibroblasts; probably because of the degree of undifferentiation of these cells, their myoepithelial nature has not been confirmed by electron microscopy (1).

The occasional finding of portions of the tumor resembling the eccrine spiradenoma is also significant. It is my belief that the eccrine spiradenoma has an identical anlage to the tumor under discussion. It appears to be a more undifferentiated neoplasm. Its cells are probably more primitive and do not seem to have the capacity to produce or induce the production of abundant hyaline.

I make a plea that the term cylindroma be discarded for this neoplasm for the following reasons. Firstly, the term is often confused with the cylindroma of salivary gland origin which is always malignant and often extends to skin. Secondly, in no way do the epithelial cords resemble cylinders. The neoplasm is composed primarily of anastomosing epithelial cords of various non-geometric shapes and sizes. I propose that the lesion be termed hyaline eccrinoma. This appellation not only points to its origin from the eccrine gland, but also differentiates it from the eccrine spiradenoma which is devoid of a conspicuous hyaline sheath, a consistent and prominent feature of the lesion under discussion. I also believe that future investigation will probably disclose that the myoepithelial cell is the primary cell of origin of this tumor as well as the eccrine spiradenoma.

My investigation does not support origin from the pilary complex including apocrine structures. Although some tubular structures resemble eccrine ducts, I believe that origin from eccrine duct anlagen is unlikely. It seems more credible and less complex to believe that the primitive epithelial cells comprising this neoplasm are attempting to recapitulate only one portion of the eccrine apparatus–the secretory segment.

Stromal proliferation about tumor lobules has apparently not been described by others and was a prominent feature in all cases. Its pathogenesis is probably similar to that observed about many basal cell carcinomas.

Although all of my patients were women, the series is too small to determine incidence. It has been stated (2) that females are affected about twice as frequently as males.

Summary

A histologic analysis of six so-called cylindromas has been performed. Results indicate origin from the secretory segment of the eccrine apparatus. Stromal proliferation about tumor lobules was a prominent feature in all cases. It is recommended that this lesion be termed hyaline eccrinoma. The myoepithelial cell might possibly prove to be the primary cell of origin of this tumor as well as the eccrine spiradenoma.

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Amitriptyline Induced Hyponatremia: A Case Report

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Hyponatremia, as a result of inappropriate secretion of antidiuretic hormone (ADH), can occur occasionally as a side effect of various psychotropic medications having a tricyclic structure like thioridazine (3) and tricylic antidepressants (1, 4, 5).

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is characterized by hyponatremia and serum hypotonicity with relative urine hypertonicity in the presence of normal adrenal, cardiac and hepatic function (6).

The following patient treated with amitriptyline is, to our knowledge, the first report of hyponatremia as a result of SIADH, associated with amitriptyline administration, appearing in American psychiatric literature. The manufacturers of Elavil (amitriptyline) have had three reports of SIADH associated with the drug, appearing in medical literature.

Case Report

A 66-year-old white, married, recently retired, woman was initially admitted to the medical service of Elmhurst Hospital in April 1977 after an overdose of chlorpromazine. After a few days, she was discharged for follow up care in a psychiatric clinic where she was placed on desipramine. In August 1977, she was again admitted to Elmhurst hospital with an overdose of diazepam. She was initially treated in the intensive care unit and later transferred to the psychiatric service with a diagnosis of manic depressive illness-depressed type. She was given oral Elavil on August 20, 1977 with 50 mgs in the morning and 100 mgs at night. She improved rapidly and was discharged after one month to be followed up in the Mental Hygiene Clinic. Ten weeks after she started on amitriptyline, she felt very weak and sustained a fall at home and was brought to the hospital on October 31, 1977. At that time she was described as confused and lethargic. Physical examination, including neurologic examination, was within normal limits except for a hematoma of the scalp in the left parietal region.

Laboratory data during admission showed a serum sodium of 112 mEq/L, serum osmolality of 236.4 mOsm/L, urine sodium of 123 mEq/L and urine osmolality of 427 mOsm/L. (Table I). Amitriptyline was discontinued from the time of admission and she was treated with fluid restriction.

Other investigations performed during the hospitalization were complete blood count, VDRL, T3 and T4 for thyroid function, serum cortisol for adrenal function, serum screening for atypical antibodies, x-ray of the chest and skull, spinal tap, electroencephalogram and a brainscan.

In light of the above work-up, the medical service concluded that the patient was suffering from hyponatremia as a result of SIADH, secondary to amitriptyline administration.

She improved remarkably with concomitant improvement in her serum chemistry (Table I). This rapid improvement after fluid restriction helped to substantiate the diagnosis.

After this episode of hyponatremia, she was treated for her depression with electroconvulsive therapy and was later placed on M.A.O inhibitors. She is still being treated and she remains well without any electrolyte disturbances, one year after discharge.

Discussion

The synthesis of ADH takes place in the supraoptic nucleus of the hypothalamus and its secretion from the posterior pituitary is regu-

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TABLE I

Laboratory Values During the Hospitalization with Amitriptyline Associated Hyponatremia

Date: November 1977	1	2	3	4	5	7	Normal
serum sodium (mEq/L)	112	127	131	133	135	132	136–152
serum potassium (mEq/L)	3.9	3.3	3.4	3.9	3.8	4.0	3.3–5.3
serum chloride (mEq/L)	80	87	94	99	100	98	97–112
blood urea nitrogen (mgm/100 ml)	6	10	12	14	17	13	8–22
serum osmolality (mOsm/L)	236.4				288.76		285–295
urine osmolality (mOsm/L)	427						
urine sodium (mEq/L)	123						

lated by serum osmolality and blood volume. The case reported here satisfies the criteria for SIADH (6) which include: 1) decreased serum sodium and osmolality, 2) continued excretion of sodium in the urine (often increased), 3) urine which is less than maximally dilute, 4) no evidence of dehydration, 5) normal renal, adrenal, cardiac and hepatic function, 6) no history of water intoxication, 7) increased ADH in the serum, and 8) correction of the electrolyte imbalance by fluid restriction. The diagnosis of SIADH is made indirectly since ADH is not routinely measured. (4)

The exact mechanism of the action of amitriptyline in the production of SIADH is not known. Lewis, who reported hyponatremia with amitriptyline therapy in hypertensive patients, believes that the hyponatremia is caused by overhydration secondary to a large fluid intake from the dryness of the mouth (7). Luzecky et al (4) reported a case of SIADH associated with amitriptyline administration in which the hyponatremia was thought to be caused by SIADH. According to Appel et al (5) amitriptyline along with other antidepressants of the tricyclic group increase the sphincter tonus of the urinary bladder and reduce the intravesical pressure. These findings together with the previously confirmed local anaesthetic effect on the bladder mucosa and a central antidiuretic effect, explain the disturbance of water balance and micturition occuring under treatment with these substances.

In April 1978, Peterson et al (8) reported a case of SIADH, that they believe to be secondary to administration of tranylcypromine sulfate, a monoamine oxidase inhibitor. There were no published reports of such a side effect with MAO inhibitors at the time when our patient was placed on tranylcypromine. She remains well at the time this report is written, without any such side effect even though she is still being treated with tranylcypromine.

The question remains unanswered why a patient develops SIADH after a particular medication like amitriptyline and not after some other medication like tranylcypromine, which is also known to produce SIADH. Our patient did not develop symptoms of SIADH when she was placed on desipramine or tranylcypromine, but she developed the same when she was placed on amitriptyline. Likewise, the patient reported by Peterson (8) developed symptoms of SIADH when he was placed on tranylcypromine and not when he was on amitriptyline. This raises another question can a patient be started on an antidepressant which is known to produce SIADH, if the patient has a history of SIADH from some other group of antidepressants? We believe we could try one or the other medication with caution, even-though there are a few reported cases of this untoward side effect.

The patient presented satisfied the indirect requirements for SIADH described previously. (6). It was not possible to challenge the patient with amitriptyline. Direct measurements of the ADH and urinary cyclic AMP were not done. The diagnosis was substantiated by the exclusion of other causes of SIADH and the subsequent course of the patient.

Our suggestions for the prevention of this type of a complication are: 1) awareness of such a side effect, 2) periodic serum sodium estimation on patients who are on antidepressant medication and 3) awareness of symptoms of hyponatremia like weakness, lethargy, confusion and muscle twitchings in patients who are on antidepressants.

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Polyarteritis Nodosa Presenting as Acute Cholecystitis

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Abstract

Polyarteritis nodosa (PN) is a multisystemic disease characterized by necrotizing panarteritis. Few patients have been reported with initial symptoms of acute cholecystitis. A case of PN diagnosed on the basis of pathologic changes of the gallbladder is presented and the clinical implications of the findings of arteritis in a gallbladder are discussed.

Polyarteritis nodosa (PN) is a multisystemic disease characterized by necrotizing panarteritis. The affected small and medium sized arteries may have an infiltration of the intima, media and adventitia by polymorphonuclear leukocytes, eosinophils, plasma cells and lymphocytes. Fibrinoid necrosis of the media is usually present with disruption of the internal elastic membrane, weakening of the vascular wall and frequently aneurysm formation.

The diffuse distribution of arterial lesions in PN produces the protean clinical manifestations, but there are no pathognomonic signs or symptoms. Fever, abdominal pain and leukocytosis are present in up to 50% of cases (1). However, only a few patients have been reported with symptoms of acute cholecystitis or with the diagnosis of polyarteritis nodosa suggested by pathologic examination of the gallbladder (2, 3). We present a patient whose symptoms were unexplained for one year until the diagnosis of PN was made on the basis of pathologic changes of the gallbladder.

Case Report

Clinical

A 69-year-old Hispanic female was admitted to The Mount Sinai Hospital with a one-week history of fever, right upper quadrant pain, nausea and vomiting. There was no history of fatty food intolerance or jaundice. One year previously, in Puerto Rico, she had undergone right elbow amputation for severe ischemia of her hand. Since the operation, she had frequent episodes of fever up to 102°F, unassociated with other symptoms. She had also developed a rash with ulceration of her lower extremities. there was no history of diabetes, hypertension or arthralgias. She had been told that her blood contained hepatitis B surface antigen (HBsAg).

She was a febrile, well-developed adult female with a fever of 102°F, blood pressure 170/100 mmHg, and pulse 70/min. Moderate right upper quadrant tenderness was demonstrable and the liver was palpable 3 cm below the right costal margin. There was no other organomegaly. The elbow stump was well healed. A diffuse scaly macular erythematous rash covered the legs, with ulceration above both ankles.

Hemoglobin determination was a 14.0g%/100 ml, white cell count 11,000 cells/mm^3

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(1% eosinophils), erythrocyte sedimentation rate 110-140 mm/hr, alkaline phosphatase 141 (The laboratory value system [Reference Value] at Mount Sinai is 30-85 mU/ml; determination of bilirubin, SGOT and SGPT were normal. Total protein value was 6.7 gm%/100 ml and albumin 2.5 gm%/100 ml. Urinalysis was unremarkable. Antimitochondrial, antismooth muscle and antinuclear factor antibody were demonstrable. The presence of HBsAg was confirmed. Intravenous pyelogram and upper and lower gastrointestinal series were unremarkable.

She had persistent fever and abdominal pain despite intravenous antibiotics. Repeated blood cultures were negative. Oral cholecystography visualized the gallbladder and ultrasonography demonstrated two small stones in the gallbladder. An exploratory laparotomy with cholecystectomy and liver biopsy was performed.

Pathology

The gallbladder was distended, 9 cm long and 6 cm in greatest circumference. The mucosa was velvety green and the wall was markedly thickened. Two 4 mm stones were within the lumen. The mucosa was not ulcerated.

Histologically, the mucosa showed moderate acute and chronic inflammation. In addition, the small and medium sized arteries were marked by a necrotizing panarteritis (Fig. 1). The affected vessels had a thickened intima and severe infiltration of the arterial wall by polymorphonuclear leukocytes, plasma cells, lymphocytes and scanty eosinophils. The internal elastic membrane was focally destroyed. Fibrinoid necrosis was not prominent. Arterioles and veins were not affected. Medium sized hepatic arteries in the liver biopsy specimen had marked thickening of the arterial wall, fibrous proliferation of the intima and destruction of the internal elastic lamina (Fig. 2), changes of the chronic stage of panarteritis. The diagnosis of poryarteritis nodosa was made on the basis of the morphologic findings.

Postoperatively, she developed a peripheral neuropathy and a low grade fever persisted. She returned to Puerto Rico.

Discussion

Polyarteritis nodosa is a multisystem syndrome which can affect any organ. Involvement of the kidney (60%-85% of cases), and of the heart 48%-100% of cases) produce death in most patients. Other organs are involved less frequently: gastrointestinal tract 47%-70%; liver 46%-65%; nervous system 8%-52%, and skin 25%-27%. Even though the gallbladder shows vasculitis in 10%-40% of cases at autopsy, only rarely has the disease been reported as presenting as acute cholecystitis. Diagnosis of this disease by examination of the gallbladder is particularly rare.

In most of the reported cases, acute inflammation of the gallbladder mucosa was present despite the absence of gallstones. The inflammatory changes in our case are unlikely to be due to stones obstructing the cystic duct because the gallbladder visualized on oral cholecystography. The presence of vasculitis in the liver biopsy (taken away from the gallbladder)

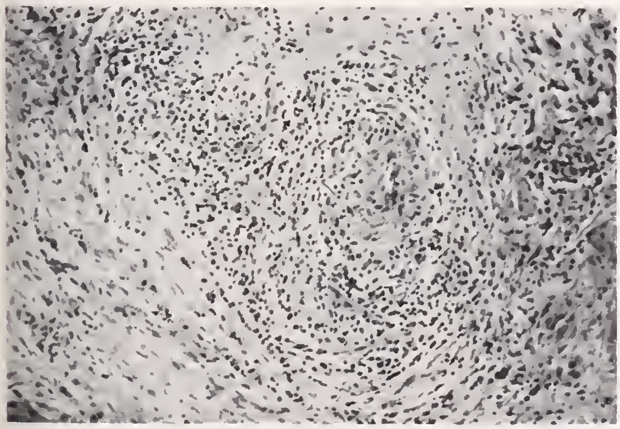

FIG. 1. Medium sized artery in the fundus of the gallbladder showing panarteritis (Hematoxylin and eosin 100× original).

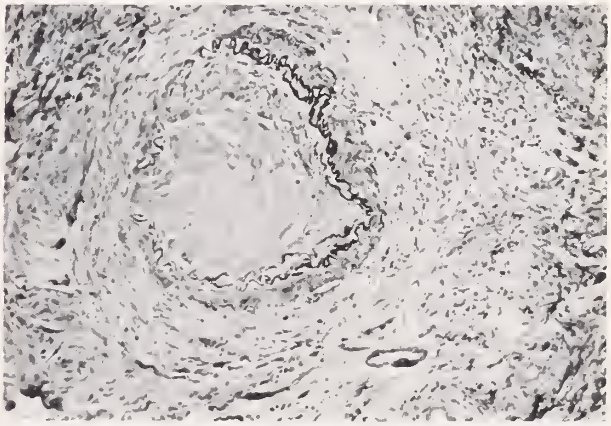

FIG. 2. Medium sized hepatic artery showing fibrosis and destruction of elastic lamina (Elastic van Gieson 100× original).

supports the diagnosis of polyarteritis nodosa as the etiological mechanism. The presence of hypertension, the history of amputation of an ischemic upper extremity, and the subsequent development of peripheral neuropathy also support the diagnosis of a systemic process.

The presence of HBsAg in our patient is of interest. It has been observed in 25%–40% of patients with necrotizing vasculitis (4). Immunoglobulins and complement can also be present in the vascular lesions. It has been postulated that circulating HBsAg-anti-HBsAg immune complexes, present in these patients, deposit in the vessel wall and provoke an immune response (4).

No etiologic association other than HBsAg has been consistently made in patients with PN. Drugs, such as sulfonamides, penicillin, and arsenicals have been associated with the development of hypersensitivity type angiitis affecting smaller arteries and veins. However, methamphetamine abusers have developed lesions identical to those found in PN. Other diseases including: systemic lupus, scleroderma, dermatomyositis, mixed cryoglobulinemia, and Sjogren's syndrome have vascular lesions with deposition of immune complexes. However, they do not produce a panarteritis with fibrinoid necrosis and destruction of the arterial wall with aneurysm formation.

The unexpected recognition of vasculitis in common specimens such as a gallbladder with cholelithiasis and cholecystitis is important because early treatment of patients with PN with corticosteroids has improved their prognosis dramatically. Death due to renal or cardiac failure (5), cerebral hemorrhage, or gastrointestinal complications occurs in as many as 66% of untreated patients within one year of diagnosis. Therapy with corticosteroids may result in a 57% five year survival. The acute vasculitis may not recur in patients with HBsAg associated PN who survive the initial acute phase of the disease (6).

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Small Bowel Pseudotumor: Case Report of an Often Forgotten Entity

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Abstract

Although small bowel abnormalities can mimic abdominal and/or pelvic tumors on both physical and radiographic examinations, this is often overlooked. A case of a 41-year-old woman with small bowel pathology that mimicked a pelvic tumor reemphasizes this problem.

Case Report

A 41-year-old black female was admitted complaining of acute onset of suprapubic and left lower quadrant pain accompanied by nausea and vomiting.

The past medical history was remarkable for total abdominal hysterectomy for leiomyomata three years prior to admission and right oophorectomy for pelvic inflammatory disease thirteen years prior to admission.

Physical examination revealed the abdomen to be tender to deep palpation. A fist sized mass in the left adnexal region was felt on pelvic examination. Plain film examination of the abdomen disclosed a nonspecific gas pattern with a soft tissue mass in the pelvis. A small bowel loop filled with air was projected within this mass (Fig. 1). The intravenous pyelogram revealed a mass impression on the superior aspect of the bladder. A loop of small bowel was again seen to be fixed above the bladder (Fig. 2). Barium enema revealed the sigmoid superiorly and posteriorly deviated by this mass (Fig. 3).

The patient was sent to surgery with a presumptive diagnosis of a left adnexal mass, rule out ovarian remnant syndrome. During surgery a moderate amount of serous fluid was found in the peritoneal cavity. The pelvic mass felt previously was a two foot loop of ileum held deep in the pelvis by band adhesions. Upon mobilization, the bowel was purplish without any evidence of viability. It was resected and the patient did well after surgery.

Pathologic examination of the resected small bowel revealed acute hemorrhagic infarction without evidence of primary vascular disease.

Discussion

Mechanical small bowel obstruction due to a simple band across a single segment of bowel does not usually cause compromise of the vascular supply to the small bowel. When an adhesive band crosses the afferent and efferent limbs of a loop of small bowel, or because of volvulus, the vascular supply is more likely to be compromised causing a strangulating obstruction. Such a devascularized loop of bowel behaves as a hemorrhagic infarction. The serosa gradually discolors to dark red, then blue, and eventually becomes black and gangrenous. The mucosa is thickened because of edema. Fluid runs into both the peritoneal space and the intestinal lumen from this loop. Gradually the isolated loop increases in size and may be succulent and tumor-like and present as a pseudotumor (1). Ulcerations and necrosis develop and finally perforations occur.

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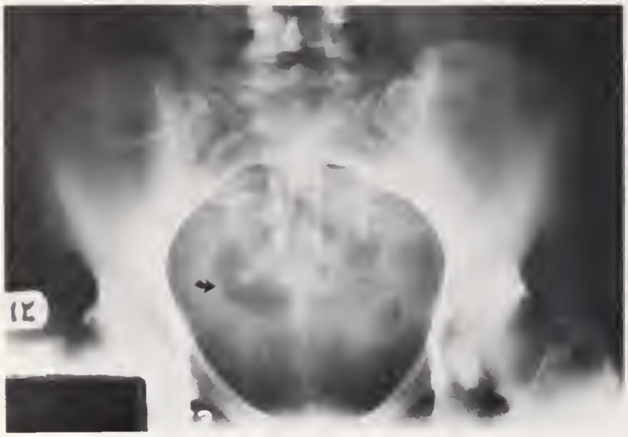

Fig. 1. Plain film of the pelvis reveals increased soft tissue density with an overlying angulated small bowel loop (arrow).

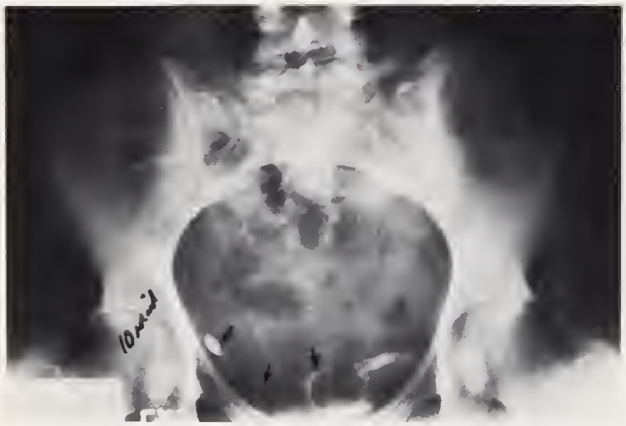

Fig. 2. During the intravenous pyelogram a mass impression is noted on the superior aspect of the bladder (arrows). the same fixed small bowel loop is again evident. A Folley balloon catheter is in the bladder.

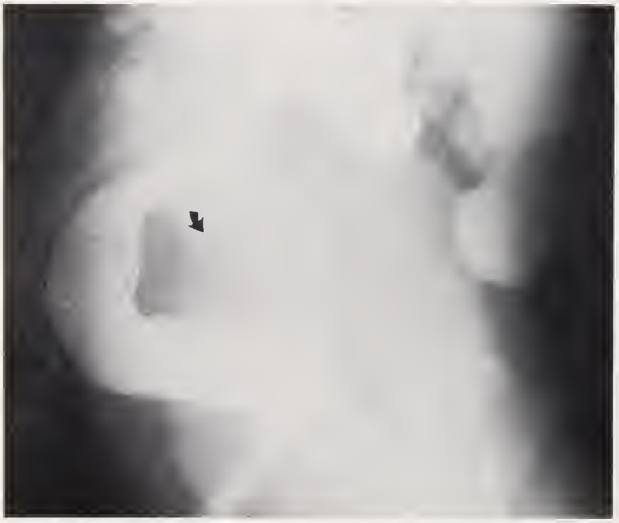

Fig. 3. Lateral film of the rectum during barium enema reveals superior and posterior deviation of the sigmoid colon by the soft tissue mass. The fixed air filled small bowel is faintly seen (arrow).

Various clinical investigations have emphasized that a strangulated loop may contain considerable quantities of fluid and feel like a cyst or tumor. A strangulated loop in the lesser pelvis can easily be mistaken for a twisted ovarian cyst or even a solid tumor.

The roentgen findings of strangulating obstruction are often scanty on plain film. Due to a general ileus of the gut, only a small amount of gas may accumulate in the loops proximal to the stenosis and only a few short air/fluid levels may be visible. The fluid-filled incarcerated loop may appear as a tumor-like density often with a polycyclic outline. This pseudotumor is most often seen in the mid abdomen or pelvis. In many cases this tumor is palpable and may give the impression of being cystic. But in some cases it feels like a hard solid tumor, clinically impossible to differentiate from a twisted ovarian cyst or even a leiomyoma. If the patient is examined in the upright position, a short fluid level may be disclosed within the tumor. The findings should raise suspicion of a strangulation (1). Suspicion of strangulation should increase if a tumor-like mass with a very short air/fluid level is seen with a polycyclic or lobulated contour. The lobulated border indicates that the fluid is within a coiled strangulated loop which is an aid in differential diagnosis. The tumor-like coil of incarcerated loops may also be appreciated if it deforms the bladder shadow on plain film or after intravenous urogram. A slight impression of the ureters laterally may also be seen (2).

Pseudo-tumor associated with strangulating obstruction is slightly more common on the right and also in women in their thirties or forties who have had abdominal or pelvic surgery, as in the case presented (3).

The major differential diagnoses to be considered are twisted ovarian cyst and mesenteric artery occlusion without obstruction. The twisted ovarian cyst is usually better delineated and roentgenographically denser than strangulated intestinal loops. The cyst has a smooth border compared to the lobulated border of intestinal strangulation.

Acute complete infarction of a segment of bowel will sometimes result in inflammatory thickening of the intestinal wall and its surrounding fat to an extent sufficient to produce a mass which may be palpable or visible on roentgenograms (4). Localized distention of the intestines to the region of the splenic flexure simulating mechanical obstruction has also been described in mesenteric artery occlusion (5). Differential diagnosis depends here on seeing marked thickening of the walls of the gas-filled intestinal loops as they parallel each other, like a cluster of bananas, which occurs in mesenteric occlusion.

In conclusion, various small bowel abnormalities may mimic lower abdominal or pelvic tumors both on physical examination and x-ray. The past history of previous surgery and the roentgen finding of a fixed air-filled small bowel loop in association with a pelvic mass should suggest the distinct possibility of intestinal pathology.

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Infected Abdominal Aortic Aneurysm: A Case Report

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Physicians have been aware of mycotic or infected aneurysms as a clinical entity since William Osler's report in 1885 of a patient with multiple abdominal aortic aneurysms secondary to bacterial endocarditis (1). Although the advent of antibiotics has done much to decrease their incidence, infected abdominal aortic aneurysms frequently present diagnostic and therapeutic dilemma.

Several pathogenic mechanisms are responsible for the development of this entity. In Osler's era, thrombo-embolic phenomena from bacterial endocarditis were responsible for most infected aneurysms. A second mechanism involves the extension from an adjacent infectious process either directly or via lymphatic vessels. This is the pathogenic mechanism responsible for most tuberculosis aneurysms. A third mechanism involves hematogenous seeding of the arterial wall during bacteremia from a distant focus other than the heart. The site of the distant focus frequently remains undetermined.

A discussion of infectious aneurysms is frequently confusing because of imprecise nomenclature. Jarrett (2), has recommended that the term "mycotic aneurysm" be replaced with the term "infected aneurysm" because bacteria rather than fungus is responsible for most infections. The infected agent can seed a preexisting aneurysm, or less frequently, infect a non-aneurysmatic arterial wall preceding the formation of the aneurysm. Frequently, an infected aorta will rupture prior to aneurysm formation.

Case Report

This was one of numerous admissions for a 70-year-old hypertensive diabetic female with a chief complaint of increasingly severe bilateral claudication. At the time of admission, the patient had a bilateral, one-half block claudication. A translumbar aortogram, performed on admission, demonstrated bilaterally obstructed superficial femoral arteries with fair run-off bilaterally. No evidence of an abdominal aortic aneurysm could be found in this examination. Since the saphenous vein was found to be of inadequate lumen, a right lumbar sympathectomy and right common femoral artery to right popliteal artery bypass was performed using Gortex graft. Postoperatively, a palpable dorsalis pedis pulse was present and the patient was discharged eight days after surgery. Three days later, she was readmitted with evidence of a superficial right groin infection. After six weeks of treatment consisting of local care of the wound, the patient was discharged in good condition. A week later the patient was readmitted because of fever, chills, and severe back pain. Blood cultures drawn at this time grew pseudomonas aeruginosa and the patient was placed on carbenicillin and metilnicin.

A heart murmur was first noted four days after admission. An echocardiogram was unrevealing. Gallium and bone scan were inconsistent with septic arthritis. While the source of the sepsis remained obscure, the fever defervesced and the patient maintained a normal white blood cell count on the antibiotic regimen. Two weeks after admission, almost three months after the initial femoro-popliteal procedure, a pulsatile abdominal mass was noted and the patient began to present spikes in temperature up to 39°C.

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Blood cultures at this time grew pseudomonas aeruginosa. Blood cultures drawn in the interim had been negative. A diagnosis of infected abdominal aortic aneurysm was made and surgery was judged necessary. At operation, a severely inflamed aneurysm measuring 8cm in diameter with dense adhesions to the surrounding tissues was found. Aortic aneurymectomy was performed and an aortobiliac woven dacron graft was inserted. Examination of the specimen showed an atherosclerotic abdominal aorta with complete destruction of the elastica. Cultures of the aneurysmal wall grew pseudomonas aeruginosa. Postoperatively, the patient remained febrile and blood cultures from the ninth postoperative day again grew pseudomonas aeruginosa. On the 13th postoperative day, the patient developed a cardiac arrhythmia and expired.

Discussion

The diagnosis of infected abdominal aortic aneurysm is frequently difficult and challenging. While a significant percentage of patients present fever and a palpable abdominal aortic aneurysm, it is quite common for patients to simply present fever of unknown origin. Under such circumstances, diagnosis will be made only after a prolonged hospitalization and work-up. Thus, Davies (3), reported three cases of infected abdominal aortic aneurysms which took from two weeks to one month to be diagnosed. Jarrett (2), reporting on 17 consecutive cases of infected abdominal aortic aneurysms states that six patients (35%) presented a fever of unknown origin and only nine patients (53%) had a palpable aortic aneurysm on admission. Three patients (17%) presented fever, back pain, and erosion of their lumbar vertebrae.

When the diagnosis is not apparent on admission, it is important for the physician to maintain a high degree of suspicion and perform serial physical examinations. Many patients with infected abdominal aortic aneurysms will develop a palpable abdominal aneurysm only after weeks or months of observation. The presence of an uncalcified abdominal aortic aneurysm should also alert the physician to the possibility of an infected aneurysm (2). The diagnosis can be facilitated by sonography and/or angiography.

The treatment of infected abdominal aortic aneurysms is always surgical. While antibiotics are an essential part of the therapy, they alone cannot eradicate the infection. Resection of the infected portion of the abdominal aorta is absolutely required. The best method of reconstructing or bypassing the abdominal aorta remains controversial.

For aneurysms infected with Salmonella, Jarrett (2), recommends bypass grafting through clean tissue planes with excision of all infected tissue. He states that strong consideration should be given to such a procedure for other Gram-negative infections and believes anatomic bypass grafting with debridement of the retroperitoneum remains appropriate when dealing with Gram-positive infections.

The aggressive nature and persistence of Salmonella infections of the abdominal aorta is highlighted in Mendelowitz's review (4). Seven patients with abdominal aortic Salmonellosis survived anatomic aortic bypass grafting only to die of recurrent infections, anastomatic disruption, or overwhelming graft sepsis.

All authors recommended a course of antibiotics in conjunction with surgery. The length of treatment may vary from six weeks to the rest of the patient's life.

The importance of the type of organism cultured from the aneurysmal wall is apparent from Jarrett's series (2). Of the seven patients with Gram-negative infections, six presented with ruptured aneurysm. Of the ten patients with Gram-positive infections, only one presented with a ruptured aneurysm. Eighty-four percent of patients with Gram-negative aneurysms died, while only 50% of patients with Gram-positive aneurysms died.

Summary

A case of infected abdominal aortic aneurysm that highlights many of the diagnostic challenges is presented. The patient was admitted with back pain and fever of unknown origin. Only after a prolonged hospitalization and work-up was the diagnosis established. In retrospect, a wound infection from previous surgery probably represented the septic focus which seeded the aorta. After the diagnosis was established, the patient underwent resection of her abdominal aortic aneurysm with insertion of a dacron graft. The patient did poorly and she died on the 13th postoperative day.

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Anomalous Phrenic Nerves in a Patient with Congenital Absence of the Left Pericardium

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Abstract

A patient demonstrated roentgenographic, electrocardiographic, and echocardiographic evidence of an atrial septal defect. Cardiac catheterization confirmed this diagnosis. At surgery, it was also discovered that the patient possessed an absent left pericardium with anomalous position of the phrenic nerves. The case demonstrates that the phrenic nerves should be carefully sought in patients with an absent or partially absent pericardium, lest they be inadvertently damaged by the surgeon.

Congenital absence of the left pericardium is a rare anomaly that causes no symptoms but often is suggested by the cardiac silhouette on the plain anterior-posterior chest radiograph (1) or fluoroscopy (2). Small defects in the pericardium may cause significant symptoms and signs if the left atrial appendage protrudes through the defect and becomes strangled (3), if the left ventricle herniates into the left pleural cavity (4), or if the left lung herniates into the pericardial cavity.

However, although usually symptom free, this anomaly may present a surgical pitfall for a patient undergoing sternotomy. This paper reports such a clinical situation in which division of abnormally placed phrenic nerves was avoided more by good fortune than by good planning.

Case Report

The patient, a thirty-five-year old engineer, had a moderately large atrial septal defect and a possible murmur since the age of twelve. He had no symptoms until a few months before admission when he felt pressure within the chest lasting an hour or so, usually after a difficult day at work or while under physical or mental strain.

Physical Examination

He was a normal, well nourished man with a mild pectus excavatum. The blood pressure in the right arm was 120/70. The pulmonary artery pulsation as well as the right ventricular impulse was felt at the left sternal border. The apical impulse was palpated at one centimeter to the right of the mid clavicular line in the fifth intercostal space. The first heart sound was normal; however the second heart sound was narrowly split. The pulmonic component of the second heart sound was heard louder than the aortic component of the second heart sound. A harsh early systolic ejection murmur was heard at the left sternal border which radiated to the apex, aortic and pulmonic areas, increasing with inspiration. At the apex, both a grade 3/6 murmur ending before the second heart sound and a third heart sound gallop were heard.

The frontal chest radiograph showed a normal sized heart displaced towards the left hemithorax without tracheal deviation. A prominent main pulmonary artery segment and increased vascularity in the lung fields were also noted.

The electrocardiogram showed a sinus bradycardia (rate of forty-three per minute), a primary interatrial conduction disturbance and nonspecific ST segment depressions. He had a positive stress electrocardiogram in March 1974.

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An echocardiogram (December 1974) showed paradoxical septal motion with an increased right ventricular cavity.

Right and left heart catheterizations were performed in December 1974 with the following findings.

Right Heart		Left Heart	
SVC O_2 Sat.	70.5%	LA Pressure	12 mm Hg.
IVC O_2 Sat.	80.5%	O_2 Sat.	96%
RA Pressure s/d	0/3 mm Hg.	LV Pressure s/d	140/10 mm Hg.
O_2 Sat.	88.5%	O_2 Sat.	95.5%
RV Pressure s/d	40/16 mm Hg.	Aortic Pressure s/d	135/70 mm Hg.
O_2 Sat.	89.9%	O_2 Sat.	95%

SVC = Superior Vena Cava IVC = Inferior Vena Cava RA = Right Atrium RV = Right Ventricle LA = Left Atrium LV = Left Ventricle s/d = systolic/diastolic

The left to right shunt was calculated to be greater than three to one. The coronary arteriogram showed unobstructed coronary arteries with a predominant right coronary artery. A ventriculogram showed uniform left ventricular contraction and some prolapse of the mitral valve without regurgitation.

Operation

Operative correction of the atrial septal defect was performed on March 1975. A median sternotomy was made using a midline skin incision. Excess fibrous tissue immediately posterior to the sternum (thought to be associated with the pectus excavatum) as well as the pericardium were divided in the midline. Hemostasis of the pericardial edge was achieved with electrocautery in routine fashion, but it was observed that the diaphragm contracted vigorously when the cautery was used on the pericardial edges.

A cresentric fold of pericardium projected into an interventricular sulcus in the region of the anterior descending coronary artery, the fold having a depth of three centimeters. Following the fold upwards towards the base of the heart, it was noticed that the left pleural and pericardial cavities were in communication because of the complete absence of the left pericardium. Further inspection revealed numerous small holes in the right pericardium. The phrenic nerves were sought and found embedded in the excess fibrous tissue between the sternum and the midline pericardium. They lay close to the midline and only three centimeters apart. The left phrenic nerve was in the interventricular fold of tissue as it coursed towards the diaphragm and only then was it appreciated how near the surgeon had come to inadvertently dividing the left phrenic, and how readily the right phrenic nerve could have been damaged or divided.

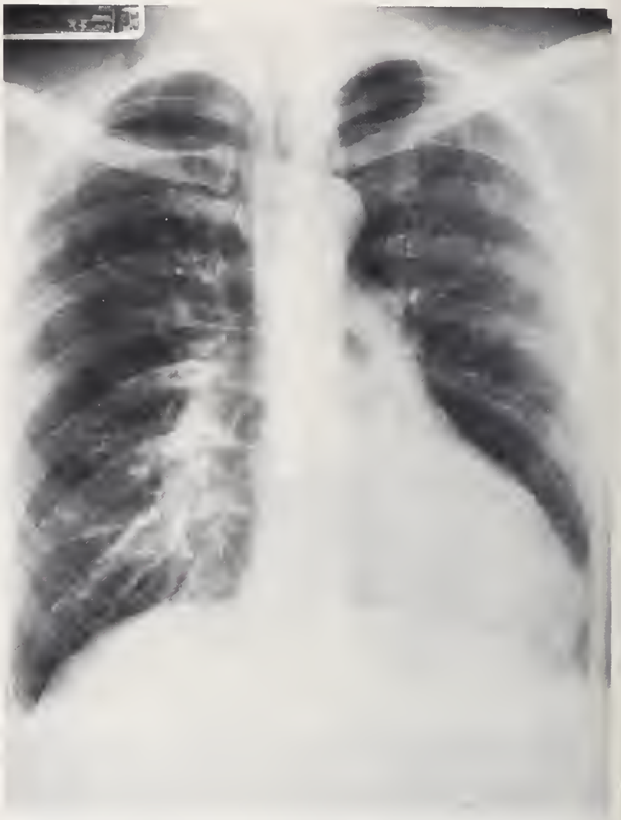

FIG. 1. Frontal chest radiograph demonstrating a prominent pulmonary artery and increased lung vascularity.

The atrial septal defect was closed with a dacron patch. The sternum was closed with wire and the skin sutured.

Discussion

When the left pericardium is absent, the anterior-posterior radiograph characteristically reveals a prominence of the pulmonary artery segment which pulsates quite vigorously on fluoroscopy (1, 2). The heart is both shifted towards the left hemithorax and rotated towards the left. However, the heart size in a case of uncomplicated left pericardial defects remains normal. Ellis et al (1959) proposed the use of a pneumothorax to establish the diagnosis of congenital absence of the left pericardium since air introduced into the left pleural space shows the separation of the heart from the diaphragmatic dome in the frontal projection and movement of the heart away from the anterior chest wall and diaphragm in the lateral projections.

The electrocardiographic features of right axis deviation and bradycardia have been documented in this condition (1, 5).

Echocardiographic findings include an enlarged right ventricle and an abnormal interventricular motion of either anterior or paradoxical motion (Type A) or flat motion (Type B) during systolic ejection (6).

The case presented here had all the above mentioned radiographic findings of congenital absence of the left pericardium. Since the patient had an atrial septal defect, confirmed by cardiac catheterization, the electrocardiogram and echocardiogram were compatible with the diagnosis of atrial septal defect and no thought was given to the possible concurrence of an absent left pericardium. Under fluoroscopy, the heart was noted to pulsate quite vigorously as is normal for an atrial septal defect, so the diagnosis of absent left pericardium was not made prior to surgery.

The pericardium has had numerous functions suggested for it, such as protection of the heart from lung infections, protection of the lungs from the beating heart, fixation of the heart in the mediastinum (1), and the regulation of the diastolic cardiac volume (1, 7-9). Pericardial defects are more commonly seen on the left side and may be the result of a deficient vascular supply to the pleuropericardial membrane (4, 5).

In the absence of the left pericardium, the left phrenic nerve has nowhere to go but into the mediastinum anterior to the interventricular sulcus behind the costal cartilages parallel with and close to the internal thoracic artery on a fibrous remnant of the left pericardium (10) or, as in this case, embedded in the fibrous tissue between the sternum and midline pericardium after having coursed for a distance in the interventricular sulcus.

The absence of the pericardium, of itself, is innocuous; however it may pose a problem when the patient has to undergo a thoracotomy. In the present case, the diagnosis of absent left pericardium was not made until the electrocautery used for hemostasis gave a clue to the abnormal anatomy. The surgeon should be careful when dissecting between the sternum and pericardium in a patient suspected of having an absent left pericardium, until the precise position of the phrenic nerves is established. For this reason the signs of absent left pericardium should be kept in mind by those performing the diagnostic studies.

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Ultrasonography of Splenic Infarct

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The ultrasonographic findings of splenic infarct have rarely been described in the literature. The main feature of a splenic infarct has been characterized as its highly echogenic nature (1). We have recently noted another feature confirmed at surgery that may be typical for the early infarct.

Case Report

A 32-year-old female drug abuser was known to have a heart murmur since childhood. She was admitted to a hospital because of disorientation and lethargy. A diagnosis of endocarditis with aortic insufficiency and parameningeal infection was made. The blood cultures grew serratia marcesens and she was transferred to The Mount Sinai Hospital, New York, for further treatment.

Physical examination at that time revealed a lethargic emaciated woman with BP 106/48 mm/Hg, pulse 111/minute, a grade II/VI systolic aortic ejection murmur, a grade 111/VI diastolic aortic insufficiency murmur, and S_3 and S_4 gallops. A tender spleen was palpated approximately 4 cm below the left costal margin. Chest x-rays revealed moderate cardiomegaly.

Laboratory Data

The BUN was 61; hematocrit was 27% with a low MCV and MCH; WBC were 8,700 with 50% bands and 36% segmented neutrophils.

An echocardiogram revealed multiple extra echoes from aortic cusps. During diastole, these echoes were numerous, had fluttering motion and appeared to continue into left ventricular outflow tract. The aortic valve orifice dimension during systole was normal (1.9 cm). The left ventricle was dilated with increased spetal motion. The findings suggested aortic

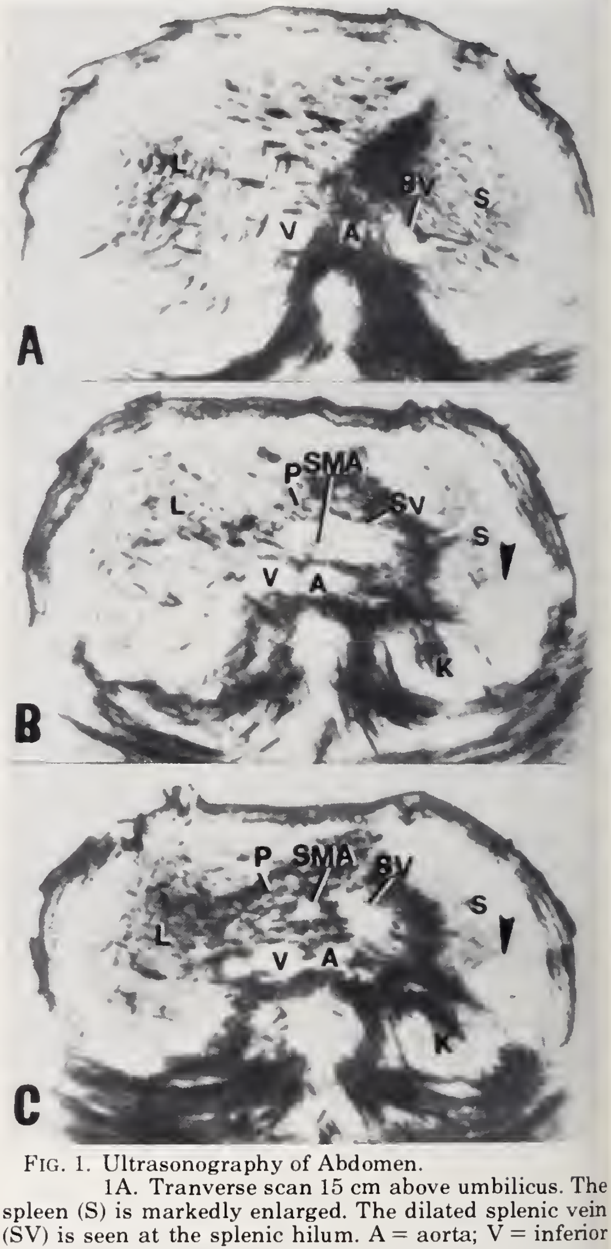

FIG. 1. Ultrasonography of Abdomen.

1A. Tranverse scan 15 cm above umbilicus. The spleen (S) is markedly enlarged. The dilated splenic vein (SV) is seen at the splenic hilum. A = aorta; V = inferior vena cava; L = liver.

1B. Transverse scan 3 cm below 2A. A splenic infarct (arrowhead) is located in the posterior margin of the spleen. Its inner border is slightly convex anteriorly. Markedly dilated splenic vein (arrows) is behind the pancreas (P). K = kidney; SMA = superior mesenteric artery.

1C. Transverse scan 1 cm below 2B. The splenic infarct (arrowhead) is more clearly seen. There is a sharp thin echogenic line demarcating the infarct from the adjacent splenic parenchyma.

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valve vegetations and/or torn aortic cusps with prolapse into the left ventricular outflow tract, and aortic regurgitation.

Abdominal ultrasonography (Fig. 1) showed a markedly enlarged spleen with a low echogenic lesion in the posterior aspect of the inferior portion of the speen, probably representing an infarct. The lesion is demarcated by a sharp thin echogenic line from adjacent splenic parenchyma. The splenic vein was markedly tortuous and dilated.

During surgery, the spleen was found to be markedly enlarged and congested and containing multiple infarcts. The splenic vein was markedly dilated. Two hundred cc of clear serous pericardial fluid were removed. The heart, especially the left ventricle, was markedly enlarged. There were vegetations in all three aortic cusps. The left and right coronary cusps were virtually destroyed, causing massive aortic regurgitation. Splenectomy and aortic valve replacement were performed.

Pathologic examination of the spleen showed that the main infarct was located in the posterior aspect of the inferior portion of the spleen corresponding to the finding in the ultrasonograph (Fig. 2). The infarct was demarcated by a zone of collagen deposit 0.8 mm in thickness. There was extensive necrosis and marked edema within the infarct (Fig. 3). The infarct was estimated to be about one-week old.

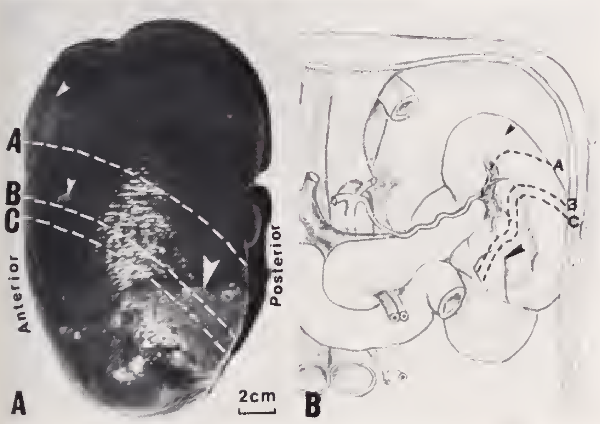

FIG. 2. Surgical Specimen of the Spleen.

2A. A large triangular infarct (large arrowhead) is located in the posterior aspect of the lower pole of the spleen. There are some other small infarcts (small arrowheads). Note the sharp demarcation of the infarcts from surrounding splenic parenchyma.

2B. Drawing showing the enlarged spleen with the large triangular infarct (large arrowheads) and small infarcts (small arrowheads) as well as markedly dilated splenic vein.

The dashed lines A, B and C correspond to the planes of sections in Fig. 2A, 2B.

Discussion

Splenic infarction is a relatively common lesion. It is almost always the result of emboli originating from the heart. In this case, the embolus most likely arose from a valvular

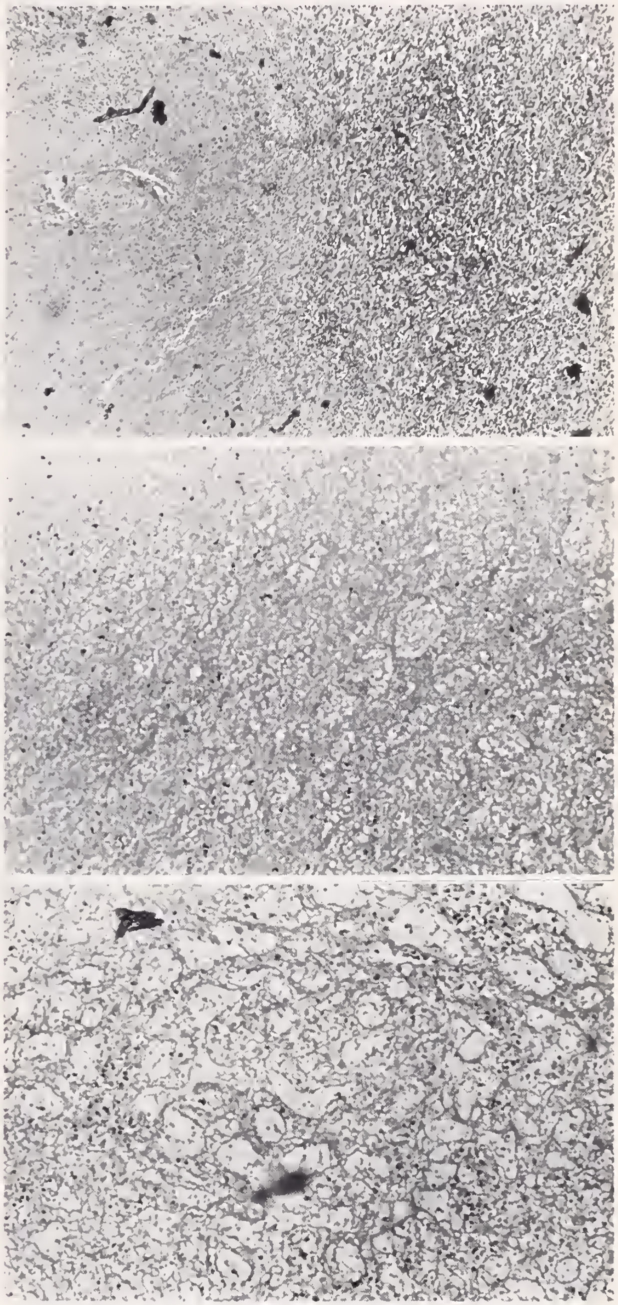

FIG. 3. Histopathology of the specimen.

3A. A low magnification view of the infarct at its border. The normal spenic parenchyma is on the right. A zone of heavy deposits of collagen fibers, 0.8 mm in width, is on the left. This represents the margin of the infarct.

3B. A high magnification view of the zone of collagen fibers.

3C. A high magnification view of the infarct showing extensive necrosis, edema and exudate in the tissue.

vegetation. The gross pathologic appearance of a splenic infarct is characteristically pale, wedge-shaped, with the apex of the wedge pointing toward the focus of vascular occlusion and its base located in the periphery (Fig. 2A)(2). Since the planes of the sonographic sections were not along the main axis of the infarct, the characteristic wedge shape with the apex pointing centrally was not reproduced on the sonogram. However, the typical peripheral location of the lesion was noted; its inner border bulged centrally. The apparent "wedge" shape of the infarct in Fig. 1B, 1C were due to the wedge shape contour of the spleen. The poor echogenicity of the lesion was caused by necrosis, edema and inflammatory exudation associated with the early infarct. This departs from the previously reported high echogenicity which was thought to be caused by chronic fibrotic changes (1) in the older lesion.

In the first few hours after onset, the infarct is somewhat poorly defined. During the next 24 hours, the demarcation between normal and infarcted tissue becomes better defined. In the course of several days, the infarcts become sharply demarcated from the surrounding tissue due to proliferative fibroblastic response in the preserved margins. This is well exemplified in our case both ultrasonographically and pathologically. The echogenic sharp thin line demarcating the infarct and normal splenic parenchyma corresponds to the zone of collagen deposit on histology. Therefore, an infarct with an echogenic line of demarcation is most likely more than several days old.

Differentiation from a tumor or an abscess may be difficult. Some tumors may be poorly echogenic (3) and abscesses with necrotic tissue debris may have some echoes. A peripheral mass producing asymmetrical enlargment or a bulging beyond the splenic contour is more likely to be a tumor or an abscess rather than an infarct. Correlation with the clinical features may be necessary.

Serratia marcesens is a rare bacterial pathogen to humans. The infection usually is associated with intravenous drug abuse or as a hospital acquired infection. The distinctive clinical features are: predominent left-sided valvular involvement, that is, aortic and mitral valves, and high frequency of embolic episodes. For mitral and aortic infections, valvular replacement is often necessary since patients often die of heart failure or brain emboli before the infection can be eradicated with antibiotic therapy alone (4).

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Surgical Therapeutic Approach to the Management of Full Thickness Burns

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Abstract

One method of burn management involves the surgical removal of the eschar material down to the deep facial plane. Skin grafting follows within a few days post-trauma. This procedure can be used in burns which, by a number of tests, appear to be full thickness in degree. The goals of this treatment include facilitation of healing and a reduction in the incidence of sepsis. At best, this is a controversial form of therapy with many risks as well as possible benefits. Criteria have not yet been established outlining indications for its use, nor have adequate studies been perfomed establishing its superiority or inferiority to "conservative" medical treatment.

Introduction

A severe burn injury can be one of the most devastating traumas that an individual can experience in terms of both physical and psychologic scarring. Although most debilitating illnesses predominantly affect the elderly, burns incapacitate both young and old. Once seriously burned, the individual faces months to years of continual treatment for both the acute and reconstructive phases of management.

For at least the past 50 years, one method of treatment for limited full thickness burns has been early surgical excision and grafting of the injured area (1). The main rationale for this treatment follows the theory of general debridement of a wound. That is, any area of dead necrotic tissue serves as a focus for infection and should be removed. In addition to removing the site of potential infection, it is hoped that prompt surgical treatment will:

1) decrease fluid loss from the wound.
2) stabilize the metabolic changes that are observed in thermal trauma.
3) decrease the time needed to heal and, as a result, shorten the interval in which the body is in negative nitrogen balance.
4) eliminate the burn's sloughing period with it's emotionally depressing bandaging procedures.

Success of these goals should reduce hospitalization time and thus improve patient morale.

In What Type of Burn Should Excision be Used?

The decision to operate on a patient can only be made with a full understanding of the natural history of burns and their healing process. Rather than define burns as first, second and third degree, it is more appropriate to label them as superficial partial thickness, deep partial thickness, and full thickness when deciding upon therapy.

Superficial Partial Thickness–This burn can involve the entire epidermal layer while sparing hair follicles, subaceous glands, and exocrine glands of the skin. These appendiceal structures are lined with epithelium. After tissue is burned, this residual epithelium will grow and spread, forming healed skin which may be indistinguishable from uninjured areas once the destroyed tissue has peeled off.

This paper was written during the author's third year of medical school.

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Deep Partial Thickness–This is also known as a deep dermal burn. Here, only the deepest elements of the epithelial lined exocrine glands remain intact. Healing is slow and the resulting skin is dense with scar tissue. Many times the appearance of the fresh wound is red or pink. It is possible for this type of burn to develop the complications of a full thickness burn if it becomes infected.

Full Thickness Burn–This is the most severe burn type, resulting in the destruction of the entire "skin," leaving no remaining epithelial derivatives. Physical appearance may vary from brown, black, to white or red. Thrombosed blood vessels may be seen below the charred surface. This hard surface, or eschar, will slough off in a period of time revealing deep granulation tissue that is suitable for skin grafting provided no infection is present. If grafts are not placed, the only means of reepithelialization is via the growth of skin from the extreme edges of the burned area where viable tissue exists. Collagen growth increases in the relative avascular areas which gives rise to scar tissue that will eventually contract. Thus, the product of unaided healing is deforming scars, partially reepithelialized areas at the perifery of the burn site, and raw central granulation areas that are particularly vulnerable to infection. It is the full thickness burn that remains open the longest and is most susceptible to complications. For this reason, intervention is warrented.

How Does One Differentiate Full Thickness From Partial Thickness Burns?

In 1943, Dr. James Dingwall wrote an article advocating the use of sodium fluorescein to determine potential salvagability of an area which has been burned (2). He experimentally inflicted full thickness burns on animals and partial thickness burns on medical student volunteers. After injecting IV fluorescein, he found that full thickness destruction remained black while partial thickness injury showed green-yellow coloration. Even in what he described as a deep dermal injury, there was still enough remaining circulation to give a mottled pattern of coloration. This study indicates that the experienced observer can differentiate various depths of thermal injury by injecting a dye into the blood stream and observing the intactness of the vasculature.

In the 1953 *British Journal of Surgery,* Dr. Douglas Jackson refutes the previously mentioned article by saying . . . "fluorescein merely showed up in the areas that possessed a circulation in the superficial dermis. During the twenty-four hours after burning, the circulation in tissue damaged by a certain intensity of heat gradually becomes arrested . . . Burns in which superficial circulation ceases during this period may have partial or complete skin destruction" (3). Rather than injecting dyes for depth determination of injury, he advocates the use of clinical judgement coupled with the parameters of wound history, site of burn, and the results of local testing for anesthesia.

Dr. Jackson found that in many instances the depth of the burn was related to the substance which had caused the injury. For example, molten metal and electrical burns are usually full thickness while high temperature liquids result in mixed scald lesions. He also noted that acid burns, although giving the impression of full thickness by their anesthetic quality, are, nevertheless, only deep dermal injuries.

Dr. Jackson observed that the locale of the burn is also important. What appear to be severe burns of the face, scalp, palms of hands, and soles of feet will heal with minimal scarring if treated conservatively. This is because skin appendages in these areas extend to levels beneath the deep dermis. Thus, the degree of anesthesia produced by a burn in these areas is not reflective of their healing capabilities.

The anesthetic quality of full thickness burns is due to the thermal destruction of free nerve endings. Dr. Jackson summarized the results of testing for local anesthesia:

1) If pain is felt upon numerous pin pricks (10/sq inch), there is only partial thickness destruction.

2) Anesthesia might be present in deep partial thick burns of the face, scalp, palms and soles of feet as well as in acid burns anywhere on the body surface.

3) Full thickness burns are always anesthetic.

Most articles do use these criteria for the determination of burn depth. However, surgeons who have experience in treating burn injuries state that even with Jackson's criteria it can, at times, be difficult or even impossible to distinguish partial from full thickness burns.

How Does Surgical Excision Prevent Infections?

Once the immediate shock and damage resulting from a burn has been survived, the major cause of fatality in full thickness injury is overwhelming sepsis. It has been shown that the superficial burn area is colonized by bacteria within three days postburn (4). Dr. MacMillan, in a study on wound management, cites that the blood stream is free from bacteria until the fifth day, with sepsis reaching a peak on the eleventh postburn day (5).

With the advent of topical antibiotics, it was possible to decrease surface colonization in the burned individual, however, the incidence of sepsis was still extremely high. Thus, another source was assumed to be the cause of the sepsis. Drs. Curtis Artz and Joseph Thompson Jr. explain that the infection originates below the eschar of dead tissue within crypts of skin and in the few remaining very deep follicles and exocrine glands (6). These structures harbor many bacteria which thrive because of decreased blood supply to the area. The vasculature becomes thrombosed with subsequent increased permeability, resulting in edema. This thrombosis also prevents normal body defense mechanisms from getting into the area. The situation is analagous to a huge pool of culture medium directly below the eschar. The size of this pool is proportional to the size of the burn.

Removal of the eschar down to a level of viable tissue and then covering the wound with grafts before the bacteria has sufficient time to multiply, theoretically should eliminate the source of infection. This is the basic premise for early excision and grafting. Even if the entire dead material were not removed, partial excision would still decrease the total size of the potential septic pool.

As antibiotic therapies have become more sophisticated, one organism has been substituted for another as the cause of death. Originally, the main invaders were streptococcus hemolyticus, staphylococcus albicans, and a variety of other bacteria including Proteous (7). These infections have been controlled and today the major offender is pseudomonas aeruginosa (8).

One antibiotic which has shown promising results is Silver Sulfadiazine. It causes complexes to form between SH groups during microbial growth, and oxidation-reduction reactions upon exposure to chloride in body fluid. In the February 1968 *Archives of Surgery,* it was shown that in experimental animals the mortality rate resulting from full thickness burns was reduced between 5%–20% when topical silver sulfadiazine was used (8).

Drs. Lloyd and Hight describe a very clever and innovative method of combining the surgical and medial approaches to prevent burn infection (9). They have found that silver sulfadiazine has an active eschar penetration of up to 1.5 mm. They proposed laminar excision of the burn area leaving only 0.5 to 1 mm of the eschar. This is followed by the application of topical silver sulfadiazine. Their results show increased survival in patients with burn injuries greater than 60% body surface area (BSA) who are high surgical risks. This method combines two effective treatment modalities while eliminating some of the major surgical risks and complications.

What Are the Major Complications of Excisional Surgery?

Complications of excisional surgery are at best synonymous with those of performing any operation on a patient who is in unstable condition. After receiving a severe burn, most patients are in some degree of shock with variable amounts of fluid loss. In addition, there is the risk of using anesthesia on a severely injured patient. These issues must be taken into account before starting any therapy. With the advent of a precise fluid replacement regime for burned individuals and the use of ketamine hydrochloride as the anesthetic, the risk of a limited excision (up to 15% BSA) has been reduced (10). However, even this procedure can result in extreme blood loss. It is estimated that an excision and grafting of only 15% BSA may cause the patient to lose more than 100% of his total blood volume (11). The patient can totally exsanguinate during a relatively limited operation.

Dr. MacMillan determined that approximately 1,500 cc or more blood is lost per 15% body surface excised (5). Thus, there is a linear relationship between blood loss and the size of the area removed. In addition, he found a second linear relationship between the volume of blood lost and the number of postburn days prior to performing surgery on a standard 15% excisional site. For each day that surgery was delayed, there was an increased 350 cc blood loss. This is attributed to a transient hyperemia that ensues in tissue that has been only marginally affected by the thermal injury below the eschar (5). A five day postponement in surgery can cause more than a threefold increase in blood loss over that of immediate surgery. In summary, if surgery is performed immediately the patient will be unstable due to the initial shock from the injury. However, a delay in order to stabilize may produce a patient who will bleed more, once the procedure has begun.

The dilemma is obvious, and there is no special formula to determine if, and when, to operate. This decision requires expert clinical judgement, weighing all considerations. Once the conclusion to operate has been reached, blood loss during the procedure can be minimized by a number of techniques:

1) Tourniquets are used when working on extremities which can survive extended hypoxic intervals without loss of function.
2) Bleeders are closed promptly with ligatures. Electrocoagulation can be used effectively, but care must be exercised. This is because even deeper layers of tissue can be burned, which may form foci for bacterial infection. This contamination would be devasting for the graft.
3) Estimation of blood loss is made by weighing used sponges and by direct measurement.
4) Large swabs are used for packing in order to produce homeostatis.

It must be appreciated that the surgeon strikes a delicate balance when deciding to do even a limited surgical procedure. If, however, burn areas larger than 25% body surface area are excised (12), the fluid and blood loss may be difficult, if not impossible to adequately replace.

Can the Surgical Approach Decrease Total Fluid Loss?

Immediately following a thermal injury, the evaporative fluid loss is equal in both full and partial thickness burns (13). This leakage is proportional to the size of the wound area. A difference in losses evolves when the partial thickness burn begins to heal at a faster rate than the full thickness injury. The eschar will remain at a high evaporative state, and thus, will continue to lose more fluid per unit area than will a healing partial thickness burn. Due to this evaporative fluid loss, the temperature of the burn patient is reduced. Even when sepsis becomes evident, the body temperature is still lower than would be expected.

Associated with this is an increase in metabolic rate. It is not known whether the fluid loss causes the increase in rate, or vice versa. However, it is understood that these changes further tax an already strained homeostatic mechanism (13).

Since evaporative fluid loss is related to the time that the eschar is present and the wound remains open, I suggest that an early removal of the burned tissue with subsequent graft coverage will substantially decrease total fluid losses and, concomitantly, metabolic rate.

Although I did not find a paper proving this hypothesis, the following articles, in conjunction with the information presented on fluid loss by evaporation, have lead me to that conclusion.

Dr. MacMillan, in a book, *Contemporary Burn Management,* writes that initial grafting for patients treated conservatively is usually begun between the 25th to 31st postburn day. By contrast, those treated surgically have their initial graft by the third postburn day (10).

In other articles, he states that when the full thickness burn is greater than 25% BSA, the autografting procedure is not completed until approximately the 100th postburn day. In the surgically treated patient with wounds greater than 25% BSA, full autografting is completed on the 39th day and the patient is discharged by the 78th postburn day (5, 12).

Since fluid loss continues from the original eschar during the entire postburn period (13), it follows from the above examples that total evaporative loss could be greatly decreased after excision of the eschar and prompt closure of the wound by skin grafts.

What About Grafting?

Following the surgical excision of the burnsite, skin grafts must be placed to create a viable covering and to prevent infection. The only permanent cutaneous coverings are one's own skin, known as autografts, or that taken from an identical twin sibling (14). All other grafts, either from human (homograft, allograft) or animal (heterograft, xenograft) donors, will ultimately be rejected. This is caused by the development of antibodies following their placement.

At the time of surgery, the decision must be made whether to close the wound permanently with autografts or to temporarily cover the site with either xenografts or, more appropriately, homografts. It must be remembered that these temporary coverings will not grow on any excisional bed which will not accept an autograft (15). For this reason, it is stated that the primary closure of the surgical wound should be done with homografts since they are expendable (15). This will prevent the loss of precious autograft material if the initial procedure is unsuccessful as a result of:

1) inadequate excision of nonviable tissue from the wound,

2) uncontrolled bleeding from the excised surface,

resulting in a hematoma or surface collection (10, 16). In essence, prior to the placement of autografts, the allografts can act as a success indicator.

More importantly, this temporary covering is invaluable when the area of the burn is so extensive as to minimize the number of sites capable of acting as autograft donors. In such instances it may be necessary to use the same donor site numerous times. An entire burn area can be closed by first using homografts, and in subsequent procedures by exchanging autografts for allografts as donor sites to recover. The rate limiting step of this endevour is the need of three to four weeks to pass before a donor site can be reused (14). During this interval the allograft can be changd every fifth day in order to avoid an actual rejection sluff which would occur if it were left in place indefinitely (16).

There are numerous sources of homograft skin available for primary closure of the existing site (14). These include fresh donor skin from a relative or volunteer and cadaver skin held in donor banks. Both these sources present viable grafts that will grow once placed on a proper site. A third source of grafting material is from cadaver skin that has been lyophilised (14). This is nonviable but can be stored indefinitely and will not promote antibody production. It is used when living grafts cannot be obtained.

Grafts can be stored at various temperatures depending upon their estimated time of use (14). These vary from 4°C when the graft will be used within three weeks to a special preparation at −100°C when long term storage is necessary. For the graft to remain viable after thawing from this low temperature, it must be dehydrated with glycerol followed by very rapid freezing.

Assuming that the surgical deficit will be closed by homograft material, the surgeon is left to determine the appropriate time for the removal of the autograft. Here the operation can be tailored to the patient's condition. Dr. MacMillan suggests the removal of sufficient autografts at the initial excision procedure in order to reduce the risks of a second induction with anesthesia (10). These grafts can be refrigerated in normal saline and then used in the future once viability of the homografts is assured. It stands to follow that if the risks of starting a second procedure are less than continuing the first, the harvesting of autograft material should be delayed. Such cases may include a patient who is unstable as a result of severe operative blood loss or an already prolonged anesthesia time due to the severity of the injury.

Conclusions

It is not possible in the scope of this paper to review the actual surgical techniques used for excision and subsequent grafting procedure. The grafting phase of management is particularly varied and tailored to each case, taking into account burn area and the availability of autograft skin. Mesh expansion and postage-stamp grafting are just two techniques used to repair the injury.

My intention has been to review a number of management problems that the physician encounters when attempting to surgically treat a serious burn. Whether the excisional approach is superior to "conservative medical" treatment is an ongoing controversy which is not readily resolved. Even the conditions for considering the various approaches have not yet been established.

Burn management is an ever changing discipline. It requires a team effort by a number of specialty physicians, each with his own expanding knowledge of clinical skills. As old questions are resolved, new ones are formed. The end result is a dynamic interplay of ideas and theories in which the final goal is improved patient care.

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Heterotopic Heart Transplantation in the Rat

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Introduction

The development of microsurgical techniques makes it possible to use small animals in the study of the immunobiology of vascularized organ transplants. Economy, the availability of inbred strains, and natural resistance to infection make the rat an ideal animal to study allograft rejection.

The kidney and heart have been the most widely studied transplant organs in rats. The latter has several advantages over the kidney: simplicity in the assessment of function, clear rejection end point, and high reproducibility of rejection patterns.

The present work details the technique of heterotopic heart transplantation in rats currently used in our laboratory.

Operative Procedures

Heart transplants are performed under a microscope using ×10 magnification; the operative steps are described below in sequence.

Harvesting of Donor Heart

The donor rat is anesthetized with Nembutal 30 mg/kg I P supplemented with ether. The thoracic and abdominal walls are shaved, cleaned with alcohol, and the animal is secured on its back on a corkboard. The abdominal cavity is entered through a midline incision and the wound edges are retracted laterally. Two mls of heparinized saline (250 units/ml) are injected into the vena cava to prevent intravascular thrombosis. One minute after the completion of the injection, the anterior thoracic wall is opened by incising the diaphragm and thoracic cage laterally along both axillary lines and then lifted. The heart is exposed by opening the pericardium. The ascending aorta and main pulmonary artery are dissected and freed from connective tissue. The aorta is transected proximally to the brachiocephalic artery origin and the main pulmonary artery is transected proximally to its bifurcation (Fig. 1). The heart is lifted and a 5-0 silk ligature is placed around the pulmonary veins and the vena cava (Fig. 2). These vessels are transected distally with respect to the ligature and the heart is removed. The harvested heart is flushed with 3 ml of cold heparinized saline solution through the ascending aorta to remove the blood left in the coronary vessels and heart chambers.

Heart Transplantation

The recipient rat is anesthetized and its abdominal wall is shaved and wiped with alcohol. After placing it on the corkboard, the abdominal cavity is entered through a midline incision. A segment of abdominal aorta and vena cava below the renal vessels is dissected and freed from peritoneum and connective tissue. Two proximal and distal loops of 4-0 silk are placed around the aorta and vena cava below the renal vessels and are used to occlude circulation temporarily during the vascular anastomosis. A longitudinal opening of 2 mm is made with Iris scissors in the anterior wall of the aorta and an opening of 3mm is made in a similar way in the vena cava. (The opening in the artery is 5–7 mm proximal to the vein in order to simplify the anastomosis). The opened vessels are flushed with saline and the anastomosis is performed end-to-side using 9-0 pro-

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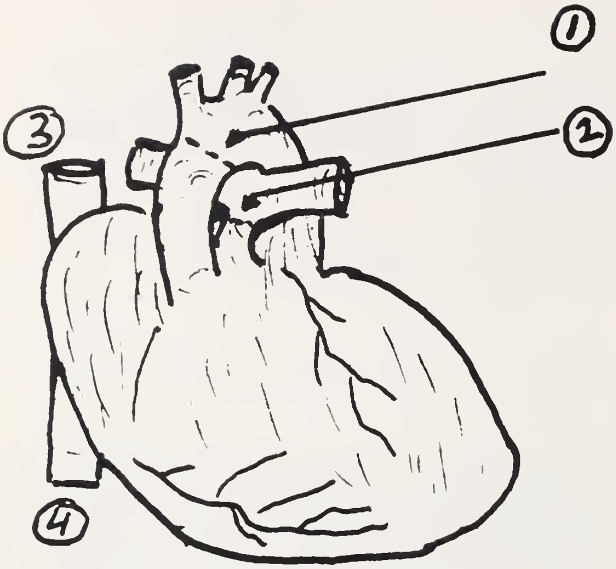

FIG. 1. *Harvesting of Donor Heart I*
The aorta (1) is transected proximally to the brachiocephalic artery origin and the main pulmonary artery (2) is transected proximally to its bifurcation (dotted line). Superior (3) and inferior (4) vena cava are shown.

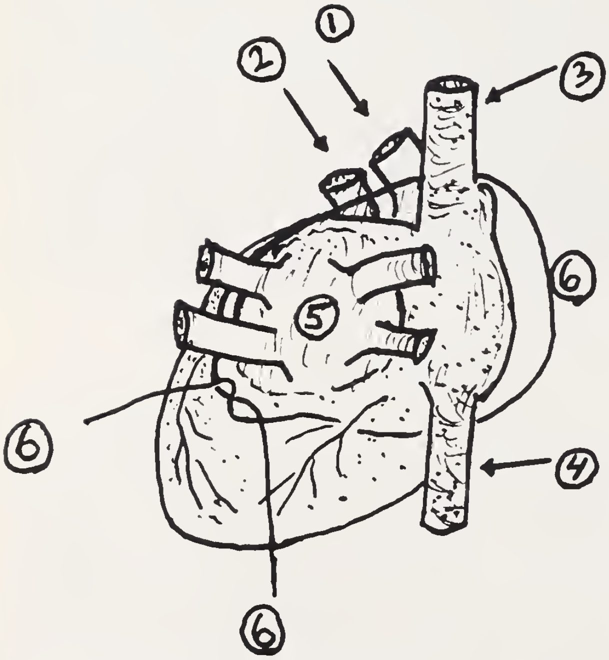

FIG. 2. *Harvesting of Donor Heart II*
5-0 silk ligature is placed around the pulmonary veins (5) and superior (3) and inferior (4) vena cava. Aorta (1) and pulmonary artery (2) are shown already transected.

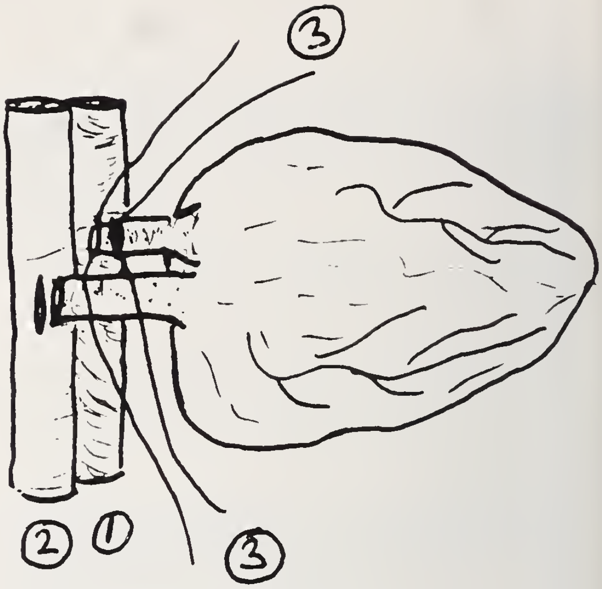

FIG. 3. *Anastomotic Technique*
Anastomosis is performed end-to-side (3) between the donor heart aorta and recipient aorta (1) and between donor pulmonary artery and recipient inferior vena cava (2) using 9-0 continuous suture of prolene.

lene continuous suture (Fig. 3, 4). Upon completion of the anastomosis, the occluding loops are removed and circulation reestablished. Initial bleeding from needle holes is controlled by applying gentle pressure with cotton swabs for one minute. The revascularized heart distends and turns pink immediately. Effective regular contractions begin spontaneously within 10–40 seconds. The abdominal incision is closed with continuous 4-0 silk suture. After surgery, the rat is allowed free access to water and food.

The heart transplanted by this method is an auxillary organ with no pump function in the recipient animal. Blood which enters the coronary arteries via the arterial anastomosis (Fig. 5) is then drained by the coronary sinus into the right atrium and subsequently into the right ventricle. Systole of the right ventricle pumps the blood through the pulmonary artery into the recipient's vena cava. The heart contractions are easily palpable through the abdominal wall. Heart function that ceases within the first 24 hours is usually due to anastomotic occlusion. If no rejection occurs, the heart continues to beat indefinitely. After 3–4 months, the heart size decreases due to disuse atrophy.

Conclusions

The development of microvascular surgical techniques has introduced an important tool in the study of the immunobiology of vascularized organ allografts. The use of the rat as an animal model in transplantation offers several advantages: the availability of inbred strains with well defined major histocompatibility an-

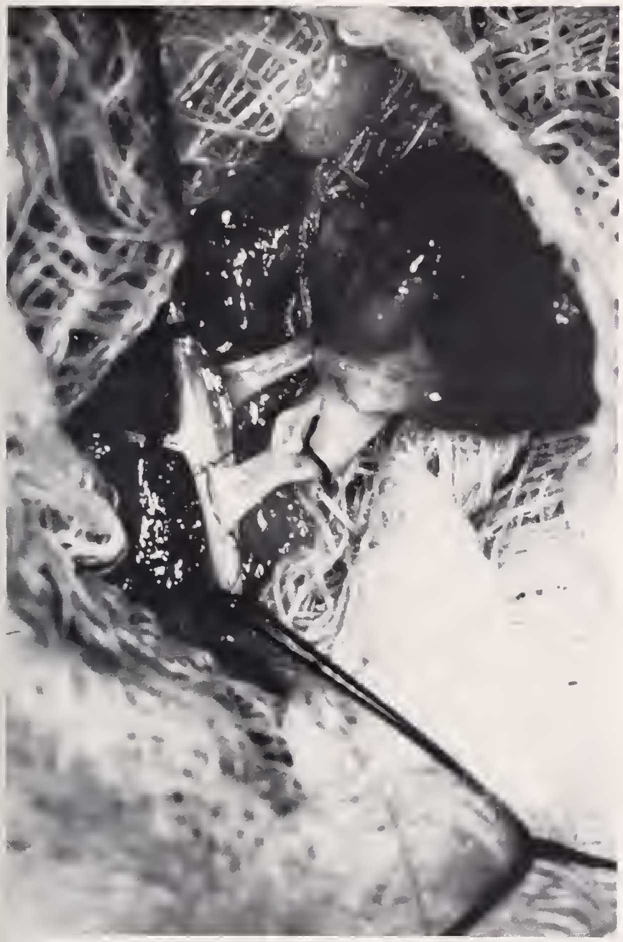

FIG. 4. *Anastomotic Technique*
This picture shows the aorto-aorto anastomosis completed and the pulmonary to cava anastomosis underway.

tigens (1), which permits the study of many different factors that can influence allograft survival, keeping constant the genetic barrier parameter, very economical with respect to animal cost, maintenance, and use of operating room space when compared with other animal models; high natural resistance to infection which makes it possible to perform surgery with clean, non-sterile instruments, greatly simplifying the experimental procedures.

Several organs such as kidney (2), spleen (3), and heart (4), have been transplanted in the rat. The advantages which make the heart transplant a procedure of choice in the study of vascularized organ transplants are:

1. After mastering the microvascular surgical techniques, this procedure is simple, fast (procedure time is two hours), and has a high degree of success (in our laboratory, the success rate is over 90%).

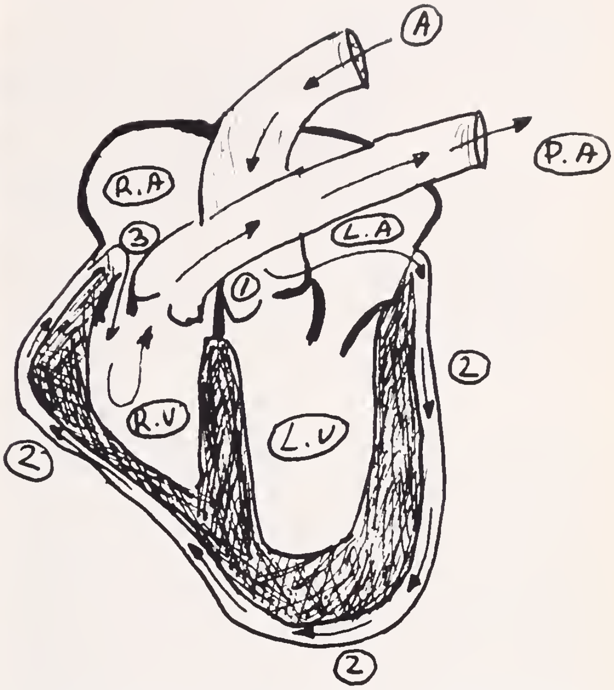

FIG. 5. *Direction of Blood Flow in Heterotopic Heart Transplant*
(1)—Aortic valve and coronary arteries origin.
(2)—Coronary arteries.
(3)—Orifice of coronary sinus and tricuspid valve.
(A)—Aorta; (PA)—Pulmonary artery.
(R.A.)—Right atrium.
(R.V.)—Right ventricle.
(L.V.)—Left ventricle.
(→ →)—Direction of blood flow.

2. The heart function and viability are determined by simple palpation and the end point for determining rejection is cessation of contractions. This is a great advantage over the kidney transplant model, where function has to be determined by BUN or creatinin measurements; the end point is death of the recipient which requires careful autopsy to rule out other causes of death.

3. When using the same strain combination, the heart transplant model is highly reproducible. In our experience, using ACI rats as donors and Lewis rats as recipients, the transplanted heart survival is 6.9 ± 0.9 days. This is clearly at variance with the kidney transplant model, where it is well known that some transplants can escape rejection and survive for a long time. The survival of kidneys is also affected by other experimental factors such as ischemic time (5), which has not been found in the heart allograft model.

All these characteristics make the rat heart allograft the model of choice for the study of the immunobiology of rejection and factors that can affect it.

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Surgical Significance of Yersinia Enterocolitica

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Yersinia enterocolitica (*Y ent*) is a small gram-negative coccobacillus classified in the family *Enterobacteriaceae.* In recent years this organism has been recognized for its clinical significance both in medical and surgical realms. To the surgeon, the role of *Y ent* in the causation of abdominal pain must be emphasized. This organism is a major cause of mesenteric lymphadenitis, particularly in children and adolescents. This condition has often been mistaken for appendicitis (1).

Initially described in 1939 (2), *Y ent* remained virtually unknown until the early 1960s when it began to be extensively studied in Europe. As late as 1966, only 23 infections had been documented worldwide (3). By now, several thousand infections have been reported, mostly from Europe, with only a limited number of cases being described in the United States (3). Yesiniosis in Scandinavia now ranks as one of the most frequent enteric bacterial infections. An estimated 10% to 15% of the patients in Denmark in 1976 who underwent appendectomies really had yersineal-induced ileitis or mesenteric lymphadenitis (1).

The rise in the number of infections identified is primarily due to increased recognition of the microorganism through diagnostic bacteriologic and serologic procedures. The low incidence rate of yersineal disease reported in the United States (only 5% of the 1978 European total) is most likely due to lack of awareness of this microorganism on the part of both physicians and microbiologists.

The genus *Yersinia* is composed of three species: *Y enterocolitica,* the plaque bacillus *Y pestis,* and *Y pseudo*-tuberculosis, a long-known animal pathogen also proven to cause mesenteric lymphadenitis and other disease in humans. The species *Y ent* has been further subdivided by surface antigen serotypes. The majority of infections are caused by serotypes 0:3, 0:9, and 0:8. Inexplicably, prevalence and distribution of these serotypes varies widely, even between neighboring regions. Serotypes 0:3 and 0:9 predominate overwhelmingly in Europe while in Canada and the United States, serotypes 0:3 and 0:8 are more frequent (3).

The mode of transmission of *Y ent* is unproven, but analogous to other enteric pathogens, the route is probably oral. There is strong suspicion that swine are the natural reservoir for the pathogenic strains (4). Food, especially pork ingestion (5) and water contamination (6), have been documented in the spread of these infections. Familial (7), school (8), and hospital outbreaks (9), presumably caused by interpersonal spread have been recorded. A large proportion of yersineal enteritis occurs in the late autumn and early winter. The organism's growth and virulence is probably enhanced by cooler temperatures. In autumn, 1976, in New York State, contamination of chocolate milk with *Y ent* caused hospitalization of 36 school children, 16 of whom had appendectomies (10). The findings at laparotomy were: Ten with enlarged mesenteric lymph nodes, four with inflammation of the terminal ileum, and four with erythema of the appendix. The period from acquisition of the microorganism to overt symptomatology was six to ten days (10).

The most frequent clinical syndrome of *Y ent* infection is acute gastroenteritis with colicky abdominal pain, and fever in the range of 38–39° C. There is frequently a mild leukocy-

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tosis with shift to immature forms. Diarrhea occurs in approximately 80% of adults (11), but in all children under five years of age. Profuse, bileous-colored watery bowel movements generally last from two days to several weeks, but chronic or recurrent diarrhea lasting several months has been reported in approximately 10% of cases (8, 12). Blood or mucus in the stool has occurred in less than 10% of the cases studied (13); polymorphonuclear cells in the stool have been documented (7). Vomiting may occur but is not usually a prominent symptom. Approximately 40% of *Y ent* enteric infections in children and adolescents involve mesenteric adenitis and terminal ileitis, particularly in the age ranges from 5–15 and 10–20 years, respectively. Severe right iliac fossa colicky pain occurs in approximately 15% of people with *Y ent* gastroenteritis between the ages of 5 and 20 years but only occasionally in older patients (11, 14, 15). Right lower quadrant pain, abrupt in onset with minimal or absent diarrhea, frequently leads to surgery and the removal of a normal appendix. The abdominal pain in this disease may arise in the right lower quadrant or may be generalized or periumbical at onset and then shift to the right lower quadrant as the disease progresses (16). In the case of mesenteric lymphadenitis, a tender, ill-defined mass of inflamed lymph nodes in the right lower quadrant may mislead the surgeon to believe that an abscess is present from a perforated appendix.

Y ent infections have also been associated with extra-abdominal systemic findings or sequelae such as: nonsupportive polyarthritis or artharalgia involving chiefly weight-bearing joints (30%–50% of adult cases) and erythema nodosum (30% of adult females) (15, 17). Iritis (17), myocarditis (15), glomerulonephritis (15), erysipelas-like eruptions (17), Reiter's syndrome (18), and hemolytic anemia (19) are other rare but documented complications. In the United States, yersineal infection has been infrequently associated with arthritis. The lack of such sequelae may be related to the absence of arthritogenic strains (0:3, phage type 8) (3). These late sequelae usually develop one to two weeks after the acute enteritis and are of no help in the initial diagnosis.

The differential diagnosis that must be considered when the surgeon assesses acute right lower quadrant pain is extensive. A list of some of the entities would include acute appendicitis, gastroenteritis (viral, bacterial, protozoal), intestinal perforation and/or obstruction, regional enteritis, diverticulitis, cholecystitis, perforated ulcer, leaking aneurysm, ruptured ectopic pregnancy, rupture or torsion of an ovarian cyst, salpingitis, ovulatory pain, endometriosis, ureteral calculi, renal pain, seminal vesiculitis, and a psoas abscess. However, with the aid of the patient's symptoms, a physical finding and radiographic studies (including plain films and contrast studies of the gastrointestinal, biliary and urological tracts) when indicated, the list of possible diagnoses is narrowed considerably.

Nevertheless, the preoperative diagnosis of acute appendicitis is incorrect in 10% to 15% of the cases (20). The misdiagnoses in order of frequency are: acute nonspecific mesenteric lymphadenitis, no gross organic pathology found at laparotomy, pelvic inflammatory disease, twisted ovarian cyst or ruptured graffian follicle, and acute gastroenteritis. In children, Meckel's diverticulitis and Crohn's disease rarely cause additional preoperative error (20). Error can occur even when the patient had a classical appendicitis history such as anexoria, followed by steady, moderately severe periumbical pain lasting 1–12 hours and then localizing in the right lower quadrant. Classically, in appendicitis, patients may have one to two episodes of vomiting only. Variations in the position of the inflamed organ produces different clinical manifestations. The only symptoms of pelvic appendicitis may be profuse watery diarrhea, slight hematuria and pyuria. However, sequential rectal examination will usually indicate developing right-sided tenderness. The anterior abdominal findings are less striking with a rectrocecal appendix and tenderness may be most marked in the flank.

Enteric *Y ent* infection is responsible for approximately 80 percent of acute mesenteric adenitis (21). Frequently the patient has a minimal history of diarrhea and abdominal pain and tenderness, particularly over McBurney's point, and rectal tenderness to the right on examination. Many surgeons speculate that, compared to appendicitis, there is no true guarding with muscular rigidity or rebound tenderness (20). The pain of mesenteric adenitis is more poorly localized and less severe (20). Surgeons have observed that the point of maximum tenderness in mesenteric adenitis is more variable in location on sequential examination, compared to appendicitis (22). The palpation of a tender, ill-defined firm mass of the right lower quadrant in a patient without signs of peritonitis, should make yersineal adenitis a consideration. These masses have been mistaken for appendiceal abscesses. A relative lymphocytosis on blood count, without a shift to immature neutrophilic cells, is suggestive of mesenteric adenitis. If a laparotomy is performed in these patients, pathology is found in the mesenteric lymph nodes overlying the ileum. These soft yellowish nodes are found to be variably enlarged, 1–8 cm in diameter, intensely inflamed and matted together in a tumor-like formation. The mesentery surrounding the nodes and the serosa of the adjacent terminal ileum and cecum are also inflamed. A small quantity of serous fluid is frequently found in the peritoneal cavity (14, 17, 22).

Histologically, these nodes show trabecular inflammation and microabscesses in the medullary region with pyroninophilic stem cells and histiocytes present (23, 24). No giant cells or granulomas are seen. Lymphadenitis caused by *Y pseudotuberculosis* can be distinguished by reticular cell proliferation, occasional granulomas gross abscess formation, and eosinophils, or giant cells, around necrotic foci (25, 26). Documented isolates from inflamed mesenteric nodes also include *Staphylococcus aureus*, *Streptococcus pyogenes*, Coxsackie, and ECHO viruses (14, 21). The latter three organisms may be suggested by a preceding or concomitant upper respiratory infection. Unusual but documented surgical manifestations of *Y ent* mesenteric adenitis include intestinal obstruction from compression by lymph nodes and a clinical picture of tenderness below the right costal arch closely resembling gall bladder disease (27).

In older adolescents and young adults, inflammation of the terminal ileum is more common but the clinical features resemble acute mesenteric adenitis. Rarely, ileitis has progressed to a fatal outcome with hemorrhagic necrosis of the ileocecal area or the entire gastrointestinal tract. There are less than ten reported cases of this unusual phenomenon and predisposing factors have not been determined (28–30). Endoscopic studies (11) in patients with acute terminal ileitis have shown the distal 20 cm of ileal mucosa diffusely inflamed, friable and edematous. Histologically, the tissue shows signs of submucosal inflammation with mononuclear cells in great numbers, particularly in the area of Peyer's patches (23, 24). Five to ten percent of patients endoscoped had one to ten millimeter diameter ulcerations of the bowel mucosa. These "aphthoid-like" ulcers are similar to the pathology of Crohn's disease, but they generally heal within four to five weeks while Crohn's lesions persist (11).

Although terminal ileitis can appear similar to Crohn's disease of recent onset, controlled studies have shown that yersineal terminal ileitis does not develop into this disease (31). Regional enteritis is rarely misdiagnosed in patients with a history of diarrhea, occasional blood-tinged stool, fever, leukocytosis, and classic radiographic studies. However, in children presenting with their first manifestations of Crohn's disease, the distinction may be more difficult. Both diseases can begin with diarrhea; so the physician must rely on the infrequency of anorexia, nausea and vomiting in Crohn's disease to differentiate it from *Y ent* infection. Morphologic abnormalities in the acute phase of Crohn's disease are minimal and consist of hyperemia and fine granularity of the serosal surface with edema and soft thickening of the bowel wall and mesentery. Moderately enlarged, soft mesenteric nodes are variably present. A fibrinopurulent exudate is invariably present on the serosal surface. Chronic disease is easily identified by gross thickening of the bowel wall with its dull purple-red color and gray exudate covering the serosa. The affected intestine has a firm rubbery texture and mesenteric fat tends to grow over the serosa so that it nearly compresses the bowel in areas of maximal involvement. At this stage, fibrosis of the submucosa and subserosa, focal aphthoid ulcers, and sarcoid-like granulomas of the submucosa clearly identify Crohn's disease.

Radiographic findings in *Y ent* terminal ileitis include diffuse thickening of mucosal folds (60% of cases), often with the presence of nodular filling defects or longitudinal mucosal ulcerations. Dilation of the terminal ileum (50% of cases) or spastic hypercontractility (25% of cases) are common abnormalities seen on bowel studies. Advanced Crohn's disease, by contrast, shows fistulization, pseudodiverticulitis, and granulomatous inflammation with fibrosis and stenosis (11).

Pathologically, yersineal enteritis may resemble inflammatory lesions caused by other agents such as *Salmonella typhi*, *Francisella tularensis*, *Brucella* species, lymphogranuloma venereum and cat-scratch disease. Bacteriologic studies are essential in distinguishing these entities but leukopenia (*S typhi*), a history of rabbit meat ingestion or exposure (*F tularensis*), or systemic lymphadenopathy (*F tularensis* and *brucellosis*) and anatomic location (cat-scratch disease and lymphogranuloma venereum) may help in the differentiation. A suspected amebic granuloma of the cecum can be diagnosed by biopsy or by visualization of the organism in stool. Approximately 85% of tuberculous enteritis localizes to the ileocecal region but this can be distinguished at laparotomy by gray-white miliary tubercles on the serosal surface.

The appendicular morphology at laparotomy in yersineal enteritis is similar to adjacent ileal pathology. Small nonspecific ulcerations are seen associated with germinal lymphoid tissue hyperplasia but there is no neutrophilic collection or serosal inflammation (24). Submucosal inflammation is similar to that in the adjacent ileum; there is no vascular compromise, abscess formation or danger of perforation.

To the surgeon, the significance of *Y ent* extends beyond its inclusion in the differential diagnosis of appendicitis and regional ileitis. Reported focal infections requiring surgical drainage include a furuncle of the thigh (32), facial and inguinal abscesses (33, 34), and an erysipelas-like syndrome of cellulitis with progression to thrombophlebitis and abscess formation (35, 36). A report of the association of this organism with *S aureus* infecting and undermining a laparotomy wound has been described (37). *Y ent* presumably spread to the wound from the appendix.

Septicemia is the rarest form of yersiniosis but it has a mortality rate of approximately 50% despite antibiotic therapy (38). Severe underlying disease has been present in the majority of septic patients. Those hosts immunologically compromised with diabetes, cirrhosis, leukemia, hepatosplenic siderosis, severe anemia and blood dyscrasias such as thallasemia or sickle cell disease, are particularly prone to yersineal septicemia (39). Sepsis has also occurred in patients maintained on immunosuppressive therapy and peritoneal dialysis (38). However, there are rare reports of septicemia in previously healthy individuals (40, 41).

Patients with septicemia generally fall into one of two overlapping clinical groups: acute and subacute. The acute septicemic form presents with pyrexia, headache, general malaise, abdominal pain, diarrhea, vomiting and hepatomegaly. Cases of blood-borne metastatic infection include a lung abscess (42), osteomyelitis (43, 44), and purulent arthritis (6, 45, 46), all of which required drainage. The surgeon is rarely able to help the patient with the subacute localizing form of septicemia which is characterized by multiple hepatosplenic abscesses and the poorest prognosis (60% mortality) (47). A history of recent diarrhea or vomiting is lacking in this insidious form which mimics amebic hepatitis with the invariable complaints of severe right hypochondrial pain, malaise, anorexia, and weight loss over several weeks (48).

Despite rigorous preoperative diagnostic efforts, a large percentage of infections by *Y ent* are first recognized at surgery. Inflamed lymph nodes, if present, should be biopsied as these will often yield *Y ent* on culture (2, 49). Drainage of the abdomen is unnecessary in these cases even if large necrotic nodes are present (50). Patients with terminal ileitis or no visible pathology, but a history suggestive of yersiniosis, should have at least three stool samples sent for culture to insure recovery of the organism. The microbiology department should be alerted to the possibility of *Y ent* as standard culture techniques designed for the isolation of *Shigella* and *Salmonella* may not isolate this organism. Special techniques such as cold enrichment of specimens and room temperature incubation of cultures must be employed to enhance isolation of *Y ent* (2, 51). At night and on weekends, specimens should be placed in phosphate buffer solution. Samples of each specimen should be incubated both at room temperature and in the refrigerator. Stool cultures are nearly always positive after the onset of the abdominal illness and will remain so for two to four months regardless of antibiotics given. Unfortunately, recovery of the organism from the stool requires 48 hours or longer and this is too long to aid in the diagnosis of the patient with an acute abdomen. Even a positive stool culture is not necessarily diagnostic of acute infection since there is an asymptomatic carrier rate estimated at 0.1%–3%. Other potential pathogens are cultured simultaneously in approximately 10% of cases (8, 21, 31).

The diagnosis of a yersineal infection may also be made by demonstrating rising serological titers. This approach, however, has not been used widely in the U.S. The antigen for serologic testing must be sought from large diagnostic centers like Center for Disease Control (52). Serologic tests are of no help in the initial evaluation of acute abdominal pain because rising titers lag approximately a week behind the onset of enteric infection (10, 21, 31). In serotype 0:8 infections, antibody titers often remain elevated for up to two years (2, 10, 17, 53). This can lead to confusion in the patient who presents with repeated enteric infections. The existence of antigens cross-reacting with members of the genera *Brucella* (54), *Vibrio* (55), and some *Salmonella* (56) species suggest that false positive results can add further error.

Since the great majority of yersineal infections are self-limited, antibiotics are not usually prescribed. The patient can be reassured that the abdominal pain will usually pass in two or three days and the diarrhea will usually clear in one to four weeks. Antibiotic therapy has not been shown to shorten the course of enteritis, mesenteric adenitis or terminal ileitis. However, most physicians recommend antimicrobials for chronic enteritis, septicemia or metastatic infection (2, 7, 10, 12, 13). *Y ent* has been shown to be sensitive in vitro to aminoglycosides, chloramphenicol, colistin, sulfonamides, tetracycline and the combination of trimethoprim-sulfamethoxazole. Many strains are resistant to drugs of the penicillin and cephalosporin groups due to β-lactamase activity (2, 17, 57, 58). Gentamicin, 1.5 mg/Kg body weight given intravenously every eight hours for two weeks has been shown to be effective in septicemia (36).

The surgeon should be suspicious of yersiniosis in any patient 5- to 20-years old who presents with right lower quadrant pain, especially if there is any history of diarrhea (8, 12, 16). There have been occasional reports of systemic illness preceding the abdominal pain and this could be very helpful in suggesting the correct diagnosis. Concomitant or preceding exudative pharyngitis which is culture-negative for β-hemolytic streptococci (59), headache (59), maculo-papular cutaneous eruption on the trunk and extremities (12), erythema nodosum (28), and uveitis (17) have all been documented with the enteritis. A history of similar gastrointestinal illness in family or friends of the patient could indicate an infectious etiology of the abdominal pain.

The differential diagnosis of Crohn's disease should also include *Y ent* infection. The two forms of ileitis can have similar pathology at initial presentation. *Y ent* may indeed be responsible for a percentage of cases of regional enteritis diagnosed at laparotomy which proceed to spontaneous remission. A routine initial work-up in patients with a compatible age and history should include cultural and serological studies for this organism.

The ability to detect *Y ent* instantaneously in a stool sample of the patient presenting with right lower quadrant pain would be of immense help to the surgeon. The technology for this exists but as yet has not been developed. Recently a heat-stable enterotoxin, similar to that produced by toxigenic strains of *Escherichia coli*, has been isolated from *Y ent* (60, 61). New experimental techniques yield agglutination of sensitized carrier particles coated with filtered supernatant fluids containing *E coli* enterotoxin (62). The carriers, either latex particles of staphylococci, are coated with specific antibody against the enterotoxin. This coagglutination technique appears to have a potential application for the immediate identification of yersineal enterotoxin directly in stool as well.

In *Y ent* gastroenteritis, it is important to isolate the patient. Attempts to locate environmental sources should be made since control measures might be effective in preventing further cases. The alert surgeon who reports cases or outbreaks and takes the appropriate samples for culture will aid attempts to further delineate the significance of this emerging pathogen in the United States. Increased awareness in this country will certainly decrease the percentage of misdiagnoses of appendicitis and unnecessary operations related to *Y ent* infection.

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Neurologic-Neurosurgical Notes

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Postganglionic Horner's Syndrome in Carotid Artery Disease

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Abstract

A patient with right Horner's syndrome and right cerebral transient ischemic episodes was found to have occlusion of the right internal carotid artery. Pupillary testing with hydroxyamphetamine showed involvement of postganglionic sympathetics. Other studies have documented Horner's syndrome in carotid artery disease but have not localized the lesion with hydroxyamphetamine testing.

Horner's syndrome of ptosis and miosis may be produced by any lesion of the oculosympathetic pathway from brainstem to orbit. Associated clinical and laboratory findings help to localize the lesion. Ipsilateral facial anhidrosis, for example, is seen with peripheral lesions proximal to the carotid bifurcation; hemicorporeal anhidrosis and long tract signs accompany central lesions. The chest radiograph may show a superior sulcus tumor. Pupillary drug tests are infrequently performed but may also add valuable information, as illustrated by the following case.

Case Report

A 52-year-old, right-handed man presented with the following symptoms: six weeks of dull right-sided headaches and facial pain, five weeks of right eyelid drooping, four weeks of intermittent left upper limb paresthesias, and two brief episodes of left-hand weakness. Aspirin 625 mg and dipyrimadole 50 mg twice daily had no effect on these symptoms. Past history included 15 years of mild hypertension.

The general physical examination was unremarkable. Blood pressure was 120/80 in each arm. There was mild right scalp tenderness. Temporal and carotid arteries were normal to palpation and auscultation. Skin temperature and sweat appeared symmetrical over the face, scalp, and axillae.

Neurologic findings were confined to the eyes. The right palpebral fissure was approximately 20% narrower than the left. Lid elevation on upgaze was preserved. Eye closure strength was intact bilaterally. The right pupil was $2\frac{1}{2}$ mm and the left $3\frac{1}{2}$ mm in moderate lighting. Hydroxyamphetamine 1% dilated the left pupil to 6 mm at one hour postinstallation, but had no effect on the right pupil. This was taken as evidence for a right postganglionic sympathetic lesion (see below).

Routine chemical and hematologic studies were normal. Sedimentation rate was ten. Chest radiograph, EEG, and cranial computed tomography with and without contrast were normal. Aortic arch study (Fig. 1) showed complete occlusion of the right internal carotid

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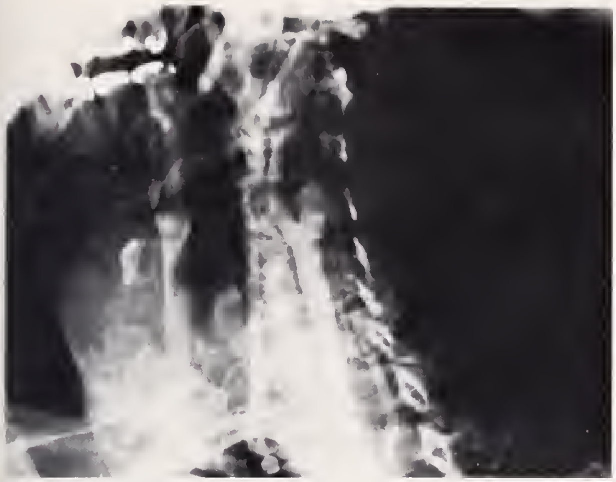

Fig. 1. Aortic arch angiogram, left posterior oblique projection, showing complete occlusion of the right internal carotid artery 2 cm. distal to the common carotid bifurcation.

artery 2 cm distal to its origin; the remainder of the vascular tree was normal. Selective right common carotid injection showed retrograde filling of the ophthalmic artery from the external circulation and faint visualization of the carotid siphon.

Patient underwent right superficial temporal to middle cerebral artery anastomosis. Postoperatively, he ceased to suffer episodic paresthesias or weakness of the left upper limb; his headache also abated. Repeat angiography three months after surgery showed a patent anastomosis with good filling of the right middle cerebral distribution. The eye findings remained unchanged.

Discussion

Horner's syndrome is infrequently reported as a complication of angiographically confirmed carotid disease, but it is seen far more often than would be expected by chance. O'Doherty and Green (1) reported 12 cases of Horner's with common or internal carotid thrombosis. Johnson and Walker (2) found miosis, with or without ptosis, ipsilateral to carotid occlusion in ten cases. Milletti (3) reported ipsilateral miosis in seven out of 44 cases of carotid occlusion. West et al described eight cases of Horner's with ipsilateral facial pain and tapering of the internal carotid artery (with or without occlusion) suggestive of dissection of the arterial wall. Biopsy in one case confirmed dissection and cystic medial necrosis. Other reports have confirmed the association between Horner's, hemifacial pain, and internal carotid dissection (5–8).

The diagnosis and localization of Horner's syndrome may be aided by pupillary drug tests with cocaine, epinephrine, or hydroxyamphetamine, as described by Thompson (9). Cocaine dilates the pupil by blocking reuptake of norepinephrine (NE) into nerve endings. Lack of dilation suggests impaired NE release due to sympathetic dysfunction, but does not localize the lesion. A weak solution of epinephrine may cause dilation of a pupil rendered hypersensitive by a postganglionic lesion. Epinephrine testing was found unreliable, however, in a large recent study by Maloney et al (10), of patients with known etiology of Horner's syndrome. The postganglionic neuron was incorrectly implicated in 55%, and incorrectly exonerated in 30% of cases. Hydroxyamphetamine ejects stored NE into the synapse, dilating the pupil unless postganglionics are affected. This drug offers a considerable improvement over epinephrine: it accurately localized the lesion in better than 90% of cases in the Maloney series (10). Only three of 81 patients with pupils inert to hydroxyamphetamine had sparing of the postganglionic neuron.

Theoretically, oculosympathetic dysfunction in carotid artery disease would be postganglionic, caused by ischemia or compression of sympathetics in the carotid plexus (1, 4). This assumption has been infrequently tested, however, and the results are conflicting. Mokri et al (5) diagnosed postganglionic involvement in two of their patients with carotid dissection; unfortunately they do not state which drugs they used to make the diagnosis. Cohen et al (6) and Davis et al (8) were unable to demonstrate hypersensitivity to epinephrine in their patients with carotid dissection. This finding argues against a postganglionic lesion, but is suspect because of the unreliability of epinephrine testing.

This patient, in contrast to the others reported, was studied with hydroxyamphetamine. Inability to dilate the involved pupil demonstrated absence of NE stores in oculosympathetic nerve terminals, indicating a postganglionic lesion. Other patients with carotid disease and Horner's should be studied to determine whether they also have postganglionic involvement.

In conclusion, carotid artery disease must be included in the differential diagnosis of Horner's syndrome. It is recommended that all patients with Horner's of uncertain etiology undergo pupillary drug testing with hydroxyamphetamine. If a postganglionic lesion is found, noninvasive carotid studies should be performed to screen for potentially dangerous and possibly treatable carotid pathology.

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Student's Corner

Benjamin Hoffman, A.B., Editor

Anterior Versus Abdominoperineal Resection for Carcinoma of the Rectum: A Literature Review

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Objectives

One of the most critical problems facing the abdominal surgeon is the choice between anterior resection and abdominoperineal resection for treatment of carcinoma of the rectum. While attempts to avoid a colostomy could in many instances jeopardize a patient's chances for cure, it is equally tragic to deprive a patient of his anal sphincter mechanism when its removal contributes nothing to survival. For carcinoma in the area of the rectum less than 8 cm above the anal verge, very few surgeons would argue against abdominoperineal resection. There is also uniformity of opinion that lesions situated more than 13 cm above the anal verge are best managed by anterior resection. However, the management of lesions in the region between 8 cm and 13 cm is a matter of some controversy.

A review of the pertinent literature was undertaken, comparing the associated morbidity and mortality as well as the cancer recurrence rates following these two procedures. Specifically, the question of whether anterior resection is the equal of abdominoperineal resection as a cancer operation for lesions in the anatomic "gray zone" was addressed.

Theoretical Considerations

Curative resections are designed to excise all tumor tissue from the primary site as well as any metastatic deposits that may be present. Therefore, for two procedures to be equally effective as a curative resection, they both must be able to affect complete removal of the gross lesion and all its extensions. Since both abdominoperineal and anterior resection are equally good procedures for removal of the gross lesion in the area of 8 cm–13 cm above the dentate line, they must then be analyzed for their ability to remove all avenues of tumor extension. Specifically, one must examine their relative ability to control the following three major pathways for metastasis of carcinoma of the colorectum: 1) invasion of the venous system 2) local extension from the origin and 3) dissemination via lymphatics.

With the venous spread of tumor, invasion of venous channels may occur at any stage in the development of the carcinoma. When this occurs, the formation of malignant thrombi and dispersion of malignant emboli make complete removal of the carcinoma impossible, therefore rendering the choice of operative procedure a moot point.

With intramural extension of carcinoma in the bowel wall, one of the more careful studies was performed by Black et al (2) at the Mayo Clinic, where 103 surgical specimens from the distal colon and rectum were studied. Multiple frozen and paraffin sections were made and subjected to careful microscopic examination,

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to determine by a pathologic study the extension of any given carcinoma in the long axis of the bowel. All grades of malignancy were included in the study. Unfortunately, only 17 specimens from the 8 cm–13 cm level were included. Nonetheless, they found that in all of these lesions, the maximum extension of carcinoma in the bowel wall was 3 mm. Of the entire group of 103 specimens, the maximal spread was 12 mm from the raised edge of the lesion. The plane of greatest extension in the bowel wall was shown to be the submucosa, and the grade of carcinoma had no relation to the degree of intramural spread.

Grinnell (10) performed a similar study but on a more representative sample: 126 carcinomas were considered, 93 of which had a lower margin of from 5 cm to 18 cm above the dentate line. The specimens were removed by either abdominoperineal, anterior, or sigmoid resection and were examined immediately after surgery. Numerous paraffin sections were prepared, the average being 42 sections per specimen. In 76 of the 93 tumors, the operation was considered curative while in the other 17, the procedure was palliative. The greatest intramural extension of tumor found in a curative resection was found to be 4.0 cm while in 67 of 76 resections, there was no retrograde spread at all. Of the palliative resections, definite retrograde mural spread occurred in nine, the maximum spread being 7 cm. Grinnell, in contrast to the previous study, did find that retrograde intramural spread was associated with more advanced tumors and appeared to be caused by the blockage of the upward flow of lymph. However, his sample size seems too small to derive conclusions about etiology. Results from the majority of other investigations in the field have borne out the findings of the above two studies. It is generally agreed that distal intramural spread is infrequent and limited in extent. When it does occur, the degree of intramural extension falls somewhere in between the results reported by Black and Grinnell. Thus, it seems that in the vast majority of curative resections, removal of the involved bowel plus a distal margin of 4 cm–5 cm of normal appearing tissue with its associated vessels and lymph supply will certainly encompass all intramural tumor extension.

The final pathway of metastatic spread to be examined is that of lymphatics. It is first necessary to consider the anatomy involved in the gross lymphatic drainage of the rectum. Below the midrectum, lymphatic drainage may be either cephaled, lateral, or caudad whereas above this level the drainage is almost exclusively cephalad (unless such flow is blocked by extensive lymphatic metastases). This dividing point in lymph flow was first demonstrated by Villemin, Huard and Montagne (20) in 1925 when, by means of dye injection techniques, they showed that lymphatic flow above the midrectal level runs into the superior hemorrhoidal-inferior mesenteric complex while drainage of bowel below this level is into the inferior and middle hemorrhoidal channels as well. Thus for lesions below approximately 8 cm, the operation must be designed to encompass all three possible routes of lymphatic drainage. This is adequately accomplished only by abdomonoperineal resection. Similarly, for lesions above the 8 cm level, the unidirectional lymphatic drainage is adequately resected by anterior resection. Theoretically, anterior resection should be at least the equal of abdominoperineal resection in terms of removing the appropriate channels of lymphatics that drain the gray zone.

There appears to be a consensus supporting the contentions that 1) above 8 cm (and probably even below this level as well) lymphatic drainage is almost exclusively cephalad and that 2) retrograde lymphatic extension is rare, is usually limited in extent, and occurs only when lymphatics draining upward in the bowel wall are blocked by node metastases. An example of one such supportive study was performed in 1946 when Glover and Waugh (9) explored the matter of retrograde nodal metastases in carcinoma of the rectosigmoid. After careful study of 100 advanced tumors in their own series and a review of others similarly studied and reported in the literature, they found an incidence of distal spread to the lymph nodes of only 3% in their specimens and 1% in the literature. In defining "distal spread," the authors claimed that malignant invasion through the bowel wall occurred in a triangular fashion and therefore only those nodal metastases greater than 2 cm below the gross lesion truly represented retrograde spread. Nonetheless, of their 3% of cases that they considered positive, only one showed nodal involvement greater than 4 cm from the margin of the gross lesion. This study is noteworthy in that Glover and Waugh attempted to secure only those specimens that represented far advanced disease so that the greatest possible spread of neoplastic cells would be contained therein. All were removed by Abdominoperineal (AP) resection to assure maximum tissue in their samples and all were at least Dukes' class C, with 99 being the ulcerative, highly malignant variety. After careful examination of many frozen sections of each specimen as well as an average of 11 nodes per specimen, they concluded that in their 3% of cases in which retrograde lymphatic spread did occur, it did so as a direct result of a block occuring somewhere across the upward channels and that the contained lymph stream was merely seeking the course of least resistance. At approximately the same time, Dukes (6) found distal spread to the nodes in 6.5% of 1500 rectal carcinoma specimens also removed by AP resection. In 4.5%, the involved nodes were located within one quarter of an inch of the tumor and in only 2% of the cases were metastases three quarters of an inch or more below the tumor.

As the above analysis indicates, anterior resection should be, at least on theoretical grounds, the equal of abdominoperineal resection as a curative procedure for lesions 8 cm–13 cm above the dentate line. Both techniques effectively remove the gross lesion in a similar fashion and, with the addition of a 4 cm–5 cm distal margin of normal appearing tissue and associated lymphatics, anterior resection should be just as complete in removing all tumor that has spread intramurally, retrograde, and to local lymphatics.

Comparative Studies

There are a number of inherent difficulties associated with the comparison of two operative procedures, especially when these procedures deal with such histologically diverse and variably extensive lesions such as carcinoma of the rectum. In addition to the variability introduced by the tumor itself, the establishment of absolutely comparable groups is further limited, especially in the larger studies, since an appreciable number of surgeons with varying degrees of technical efficiency are involved and the surgical techniques employed are not entirely consistant throughout. In addition, a bias towards abdominoperineal resection seems to be present under certain circumstances relating to the size of tumor, involvement of contiguous organs or structures, physical habitus of the patient and the experience of the surgeon. Despite these reservations, certain trends may be observed and certain inferences may be drawn.

An overview of relevant comparative studies in the area reveals the following results concerning procedure-associated survival rates.

Although these results appear uniformly favorable for selecting anterior resection, there are a few considerations to remember to more accurately interpret these findings. Since AP resection was the more utilized technique in earlier studies, the survival results may be skewed because less refined operative techniques existed at that time (13). Secondly, the smaller, more favorable lesions seemed to have been treated by anterior resection while the more advanced lesions were subjected to AP resection (5). Finally, the apparent decrease in survival following AP resection might have been influenced by the seemingly predominant use of this procedure as treatment for lower lying lesions which carry an intrinsically poorer prognosis because of their location (17). (However, Stearns (17) controlled for this effect and still came out with better results for anterior resection.) Despite the above factors, a careful examination of the studies reveals the recurrence rates after adequate anterior resection are probably no greater than after AP resection.

A detailed comparative study was performed by Williams et al (22) of the Ohio State University hospitals, from January 1950 to December 1961. He examined 182 carcinomas located between 6 cm and 15 cm from the anus, 89 were treated by anterior resection and 93 by abdominoperineal resection. A careful attempt was made to insure that the lesions represented in

Investigator	No. of Cases Studied		5-Year-Survival Rate	
	Anterior Resection	AP Resection	Anterior Resection	AP Resection
Waugh et al (21)	126	69	65.6	51.6
Deddish and Stearns (5)	150	248	69	65
Williams et al (22)	89	93	57	46
Palumbo and Sharpe (13)	76	67	57	50
Slantz et al (15)	247	277	56	47
Stearns (17)	225	227	56	48
Strauss et al (19)	49	34	55	44

both groups were comparable: the median tumor size as recorded from the pathologic specimens for each group was 5 cm and the Dukes' classification of the tumors were virtually identical. The operative procedure was somewhat standardized in that wide pelvic dissection to a level at least 3 cm below the tumor, as well as extensive mesenteric resection were performed in both groups. Postoperatively, 53% of the patients had one or more complications after abdominoperineal resection whereas only 40% had complications after anterior resection. This higher incidence of complications after abdominoperineal resection was largely caused by more frequent urinary tract problems, especially prostatic obstruction and urinary tract infection. Moreover, the operative mortality, although not statistically significant, was lower after anterior resection.

It is worth noting that there were no cases of frank fecal incontinence in any of the patients that underwent anterior resection and only one patient suffered recurrence at the suture line. Finally, of the 118 patients having curative resections, the 5-year survivals were 57% for anterior resection and 46% for abdominoperineal resection. The authors concluded that the low incidence of suture line recurrence, the equally low mortality, and the comparable 5-year-survival rates confirmed the impression of previous studies that the rectum need not be sacrificed for all lesions 6 cm–15 cm above the anus. Furthermore, the size and location of the lesion are less important than the size of the pelvis and the presence of other technical considerations in the choice of anterior resection. This procedure is comparable to abdominoperineal resection if adequate lateral and inferior dissection can be accomplished and if low anastomosis in the pelvis is feasible.

One of the most ambitious and multifaceted studies was presented in 1971 by Slanetz et al (15) from the Department of Surgery, Columbia Presbyterian Medical Center. They undertook a retrospective analysis of 524 procedures, 277 consecutive abdominoperineal resection and 247 consecutive anterior resection, performed between 1944 and 1963 for single primary malignant lesions located between 8 cm to 18 cm from the anal verge. The issues of morbidity and mortality, 5-year survival, and local recurrence were examined with comparisons made between lesions of similar Duke's classification and similar level of tumor in every category. Both anterior resection and abdominoperineal resection were found to have a 5.4% mortality for the entire 24-year period. It was interesting to note that there had been a gradual increase in mortality from abdominoperineal resection during this interval (3.5% from 1944–1950 and 6.8% from 1956–1963), while the mortality from anterior resection declined significantly during the same period (from 7.9% to 2.4%). This may be best explained by the observation that a severe physiologic stress is imposed during abdominoperineal resection–cardiopulmonary events accounted for 50% of the mortality–and that the average age of the group undergoing abdominoperineal resection has risen steadily from 56.8 years to 63.4 years. In that sepsis is the principle cause of death following anterior resection, the improvement noted must imply that there had been better management of infection, whether by more effective bowel preparation, more careful anastomotic technique, or more judicious use of antibiotics. With respect to morbidity, only 32% of the patients with abdominoperineal resection had no postoperative complications, as compared with 44% following anterior resection. Cardiovascular complications were significantly higher with patients undergoing abdominoperineal resection, and urinary tract infection or obstruction occurred in 35% of the patients after abdominoperineal resection. Wound infection, on the other hand, was encountered more frequently and was of more serious consequence after anterior resection.

With hospital mortality excluded, the overall 5-year survival after abdominoperineal resection was 47% and, after anterior resection, it was 56%. When comparisons were made according to Dukes' classification of the lesion, it was noted that a 5% superiority can be ascribed to anterior resection in each of the three categories (Dukes A, B, C). These results are somewhat prejudiced because, regardless of the pathologic classification, there has been a tendency for the surgeons to allow the size of the tumor or its degree of contiguous extension to influence their choice of procedure. This is evidenced by the observations that the average length of the primary lesion was 5.48 cm for abdominoperineal resection, as opposed to 4.60 cm for anterior resection. Also, two-thirds of the patients demonstrating ostensible extension of the tumor to adjacent structures underwent abdominoperineal resection.

Slanetz next investigated the 5-year survival relative to the level of the tumor and found that within each operative group the level made little difference in survival rates, with anterior resection having a 9% survival advantage for each location considered. He then discovered that comparison of the two procedures with respect to local recurrence fails to lend strong preference to one or the other, although the rates appear to be somewhat lower after anterior resection. It must be remembered that locally extensive lesions were managed more often by abdominoperineal resection than by anterior resection, thus predisposing the development of recurrent disease locally. On the other hand, suture line recurrence, a potentially preventable situation that occurred with an incidence of 9.1%, was included in the figures under local recurrence rates after anterior resection, thus producing some upward distortion. With both of these reservations in mind, the local recurrence rate may be assumed to be nearly identical. Finally, no clear superiority could be claimed for either procedure regardless of Dukes' class when 5-year survival was compared for male and female patients.

Conclusions

On a theoretical basis, anterior resection should be at least the equal of abdominoperineal resection in terms of total tumor removal for lesions located between 8 cm and 13 cm above the dentate line. The previously reviewed pathologic and anatomic studies indicate that a properly performed anterior resection will excise the gross lesion and all its intramural extensions as well as extirpate nodal metastases with an efficacy equal to that of the Miles procedure. This was subsequently demonstrated through a review of representative studies: anterior resection has consistantly yielded a comparable, if not better, 5-year-survival rate and a comparable, if not lower, operative mortality and morbidity than its sphincter-sacrificing counterpart. Thus, it may be concluded that the decision to perform either an abdominoperineal resection or anterior resection should be predicated essentially upon the distance of the lower border of the cancer from the anus. In cases technically suitable for either operation, there is no statistically significant difference between the two as curative procedures.

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Medical Journalism for the Layman: The Importance of Physician Input

Steven A. Gaudio, B.S. and D. DeMatteo, B.S.

Introduction

The written dissemination of medical information has developed extensively since the Sumerians introduced it in southern Mesopotamia (Iraq) in approximately 3000 B.C. (1), with treatises and prescriptions on medical diagnoses and prognoses (3–6) on cuneiform tablets (2). Medical journalism, as we know it in this country, was the offspring of numerous medical societies that began to appear or reappear following the organization of the American Medical Association (7–8). By the mid-1840's, several journals had been started in eastern cities and followed migration patterns to the West and South (9), while by 1876, thirty-one medical journals had been started in New York City alone, together with another nine devoted to specialties and six reprints of foreign journals (10). Today, there are thousands of journals, magazines, newsletters, etc., concerned with the conveyance of medical information to the layman and/or the medical professional. These periodicals serve as a forum for the presentation and discussion of varying views on controversial topics in medicine. It is the role of educating the public that we would like to discuss in greater depth.

Importance of Lay Medical Journalism

The importance of patient education through the lay press all too often is minimized, although it is difficult to understand why. Educating the lay population about proper maintenance of its health allows patients to become active participants in their medical care. This fulfills the patients' desires for such a role, documented by the publishing of approximately two thousand books of medicine for the layman in the last five years (11), together with the enormous rise of the self-care movement in this country and in Europe. Medical journalism is immensely efficient in terms of the number of people reached for the input of effort and it is vital for successful preventive medicine. It can be used to give direction and clarity to a public assessing the different medical treatments available, thus serving as an excellent method of consumer protection. As medicine is regulated and/or funded more by federal, state, and city government, it will be necessary for voters to have a better understanding of the medical field. Lay medical journalism is also valuable in dispelling unfounded antagonistic attitudes toward the medical profession.

We are not attempting to minimize the task of community education; we all are acquainted with the claim that the knowledge accumulated by man before the twentieth century has been doubled already in this century, and that it may well be redoubled in the next twenty years (12). But the rapid increase in medical information, with the inevitable eradication of former dogmas, makes it imperative for the lay press to inform the public about medical advances and health maintenance. In many aspects, the American people have never been healthier. The average life expectancy is about 73.2 years, an increase of approximately three years in the last decade. In this same time period, the number of deaths from cardiac disease and from cerebral vascular accidents has decreased approximately twenty-two percent and thirty percent respectively. Education undoubtedly has played an important role in these results (13). However, a great deal more remains to be done. About thirty percent of the patients seeing a physician should be examined earlier in

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the course of their illnesses, but unfortunately, many people do not know how to recognize their symptoms (14). The potential for the health education of the layman, which would help him to recognize early symptoms of disease and to prevent disease, is underestimated.

It is often argued that too little knowledge is dangerous and that informing the public will do more harm than good. However, two European studies showed that ninety percent of the steps (taught by physicians) that patients took before visiting their physicians were safe and relevant (15).

The Physician and Medical Journalism

Despite medical professionals' growing awareness of the importance of patient education and the influential role of the lay press, there is a relative lack of physician input into the preparation of lay articles. There is a definite need for physician input in medical journalism to insure the presentation of accurate facts, to insure that the truly important topics are presented, and to increase the validity given by the public to the content of the article.

Many newspapers and magazines assign journalists without medical training to research and write science and medical articles (16). Frequently, the untrained medical writer resorts to standardized, valueless phrases in an attempt to translate complicated terms or concepts which he himself does not understand. Premature judgment often is made on the complex results of preliminary research, resulting in sensational news reports in which "major breakthroughs" are proclaimed instead of merely describing theory and experimentation (17). Such sensational news reports lead to much of the current public confusion about health care (18), and can easily mislead readers into having misconceptions about the state of medicine today. (Of course, this must be differentiated from the phenomenon when, upon learning of reasonable medical success in the treatment of some diseases, the reader hopes for success in the treatment of all other diseases.)

The public, informed by sensational, irresponsible articles in the popular press, and by promises from untrained medical spokesmen, has begun to expect far too much from the current practice of medicine and is unhappy with anything less than their misinformed expectations. A large amount of effort and time must be used to correct the patient's misconceptions, unnecessary anxiety, and false hopes engendered by careless articles (19). Such articles are more frequent than one would like to believe, yet accuracy need not be sacrificed for reader interest. The problem can be alleviated somewhat by procuring specialists, preferably medically-trained professionals, to serve as advisors or authors of articles for the lay press. Although Simons (20) disagrees with this viewpoint, believing that a generalist (nonspecialist) can obtain the proper information for the layman, it is a well-known fact that most readers would rather learn from the experts (21). Weinberg (22) has also proposed that scientists report the recent advances in their own fields.

Conclusion

Medicine and journalism must take greater responsibility in the medical education of the community. The prevention of disease, morbidity, and mortality can be better attained if people better understand the etiologies and complexities of disease and its treatment. Medical education for the public, regardless of the specific methods used, is important for the advancement of human health. McKeown (23) agrees that this is one of the most important methods now available for development. It is for this reason that utmost care be taken in presenting medical news to the public; the medical profession shares this responsibility with the government, industry, and journalism. One of the medical journalist's most important tasks is the overall evaluation of the current and projected paths which medicine could take, based on recent political or medical developments. Because of the central role health takes in people's lives, information must be presented accurately and clearly by informed sources. One of the contemporary challenges to physicians is to help patients understand and prevent disease. Yet there exists little or no incentive for sharing this information with the layman through journalism or broadcast media other than dedication to the principle that the health and welfare of the patient comes first.

As we progress, the problems confronting medicine and the methods at our disposal for solving them will, of course, change. It may be necessary to alter how the public is educated medically, but the need and relevance for such education will still exist. In the future, carefully designed health education programs, including a more judicious use of medical journalism for the layman, will be needed to give the public the information it requires to make the most effective use of all medical resources. Currently, in health services, there is a fashionable pursuit of newness, of innovative ideas and of new solutions (24). Though such efforts are undoubtedly important, it is also vital that one examine those resources that are not being used to their fullest potential for the health and the welfare of the patient; medical journalism for the layman is one such resource.

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Editorial Statement

The Editorial staff of The Mount Sinai Journal of Medicine is pleased that, once again, we can offer our readers an interesting and educational special issue.

In 1980, MSJM celebrated the affiliation of The Mount Sinai Medical Center with the Jewish Home and Hospital for the Aged by gathering a collage of clinical and research articles from the varying medical specialities. The editorial approach, then as now, exemplifies the overall Mount Sinai management approach to Geriatric Medicine.

This year we have taken one further step. We are publishing in this November/December 1981 issue, the two-day, Fourth Annual Brookdale Medical Conference on Geriatrics. The conference was an interdisciplinary and interprofessional effort. And, by all reports, it was an enormous success, demonstrating once again that team work, collaboration, and cooperation is the best approach to growth, development, and aging.

The entire proceedings were transcribed. Several speakers contributed finished manuscript versions of their lectures. The remaining talks were edited and refined from the transcripts. The four, two-hour workshops were so immense with detail that we were forced to use summarized versions because of space limitations. We have included whatever charts or figures that were available for use.

All in all, we present an overview of Geriatric Medicine today as it is seen by physicians and allied health professionals.

We give a very special thanks to the committees, organizations, and editorial staff that have worked so hard for almost two years (pre and post conference) to bring this special report to you.

David A. Dreiling, M.D.
Editor-in-Chief

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Introduction

The fourth annual Brookdale Medical Conference on Geriatrics and Gerontology, held on December 4-5, 1980, sought to address a multidisciplinary approach to the medical and social-health status of older persons. The conference speakers were specialists in the biomedical and social sciences, researchers and practitioners, who assessed a range of medical and social problems the aging population is facing. The care of the elderly was examined for its growing impact on the health care system, its wide range of providers who serve this population either full- or part-time and its mounting costs and demands. While the conference did not address the question of who and where the elderly should be cared for, nor how we achieve an interprofessional approach to the many issues, it certainly gave recognition to the need to be more knowledgeable and more understanding of the biologic and social processes seen in aging. For those in the health field, there is recognition that no accepted theory of aging exists, nor does any organized body of knowledge governing the aging processes. What does exist is a great number of individuals committed to gerontology, the study of aging in its lifelong process, and a few who believe there is a need for a specialization in geriatrics, the diseases of aging.

This conference brought to its audience an understanding of the range of concerns that are posed and being worked on. Probably, no other area of human development and services has such a range of disciplines and professions committed to it. What becomes clear to those who work in the field is that the aging individual brings his social, psychologic and economic lifestyle to his physical status. When his chronic ailments are exacerbated, or when he faces an acute illness, the elderly person's social and environmental conditions become relevant to the illness or disability and its care. In this conference, the indications were clearly supportive of George Engel's belief that the "dominant medical model" is outmoded in serving the aged. A biopsychosocial model of care, adding the social, psychologic and behavioral dimensions to the physiologic, provides a blueprint for understanding what is happening to an individual, and a framework for research, teaching, and planning for action and social policies in the social-health care of aging persons.

What is ahead of us? Longevity continues as a challenge to American society as the public asks how to make their lives more healthy and more satisfying. Longevity remains a challenge to the biomedical and social scientists who ask whether aging has unique dimensions making it a biopsychosocial entity in the study of the human being.

The issues, concerns and planning on behalf of the elderly are many. The physical, psychologic, social-environmental, cognitive, relationships and network factors touch us all. The annual Brookdale conferences on gerontology and geriatrics are committed to opening the doors to the knowledge and services affecting the aging so that its participants may interact, share, and learn from each other. In time, these participants will have been responsible for the incremental changes in the field.

Samuel K. Elster, M.D.
Helen Rehr, D.S.W.
Co-Directors

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Preface

Thomas C. Chalmers, M.D.

(Editor's Note: Dr. Chalmers, President of The Mount Sinai Medical Center and Dean of Mount Sinai School of Medicine (CUNY) was unable to open the proceedings for the Fourth Annual Brookdale Medical Conference on Geriatrics due to a "geriatric" back ailment that required bedrest. His commitment to the fields of Geriatrics and Gerontology at Mount Sinai prompted him to send a taped message to his colleagues. We have abstracted a few of the more salient points of Dr. Chalmers' remarks.)

Disease is an equal opportunity protagonist. It can strike anyone regardless of age or sex. The symptoms and signs are the same. However, the virulence and speed of attack will vary, depending on the initial health status of the potential victim and, obviously, the person's age.

The aged individual faces greater problems with an illness, requires different treatment modalities, and has a more difficult convalescence period than a younger individual. To quote the famous British physician, Richard Asher:

> Pity the patient lying long in bed, his blood clotting in his veins, the calcium draining from his bones, his colon becoming distended with scybala, the urine leaking from his distended bladder, the flesh rotting from his seat and the spirit evaporating from his soul.

One of the principal aims of Gerontology and Geriatric medicine is to keep the aged out of bed. This is an indispensible goal for the nation as a whole. Our population is aging and the percentage of people over the age of 65 is increasing and will continue to do so well into the next century. We must devote our energies to making the quality of life better as we age.

For centuries, medical researchers and clinicians have worked to combat disease and improve standards of living. Progress crept forward until the early 1900's, when breakthroughs accelerated the pace. Oliver Wendell Holmes was right when he spoke of 100-year-old individuals. We could have them soon. We have prolonged life and now must concentrate on improving it.

Part of the aging process is system failure. Over time, we have increased trouble with the heart, the kidneys, the lungs, and the brain. If one or more of these organs fail, we have an individual in whom the quality of life could be such that "it is hardly worth living."

With the ongoing dedication of scientists in research, diagnosis, and treatment, we will be able to avert and postpone system failure, and perhaps maintain an optimal quality of life until the day when all systems fail.

In keeping with the Mount Sinai tradition of planning and preparing for the future, we are confronting the challenge of Geriatric medicine with a multipronged attack:

- Within the Department of Medicine, we have established a Division of Geriatric Medicine, designed to improve patient care and train the undergraduate medical student.
- Through our affiliation with the Jewish Home and Hospital for the Aged in New York, we are bringing the advantages of education and research to a famous patient care institution while in turn bringing skills in long-term care to Mount Sinai.
- We can also utilize the divisions within the Brookdale Center for Continuous Education and the Page and William Black Post-Graduate School of Medicine. One division is designed to educate the patient and consumer; another is structured to educate the practicing physician and the allied health professionals. Today's symposium is a fine example of education in action.
- Finally, through the generosity of the Brookdale Foundation and the Ritter Foundation we have gathered a major share of the funds necessary to attract the best professional to head an Institute or Department of Geriatrics at Mount Sinai.

We firmly believe in the interdisciplinary approach to medicine. The team work we coordinate and execute today will have far reaching impact on our society, our health, and our own future when we, too, join the ranks of the aged. Thank you.

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The Interface of Clinical and Ethical Decisions in the Care of The Elderly*

LESLIE S. LIBOW, M.D., F.A.C.P.

Abstract

The physician rendering care to the elderly is frequently faced with ethical issues that interface with clinical decision making. The prevalence of these issues has been enhanced by the demographic changes and therapeutic advances of the past decades and the recent economic pressures toward "cost effectiveness." There is already some tendency to use age as a criterion in triage situations. While being properly budget-minded, the physician must not relinquish his role as "healer" to his patient.

The ethical-clinical interface issues in care of the elderly and some suggested approaches include: triage by age, use of the "Penultimate Will," right to refuse treatment, passive euthanasia, responsibility to our patients who enter a nursing home, excess surgery, informed consent patient's choice of therapy and its relationship to age, and communicating with older patients about serious problems.

The issue is, finally, the value of human life.

"Pneumonia may well be called the friend of the aged" is one of Osler's most quoted aphorisms (1). Coined in 1909, it highlights an issue now more than ever present in the daily work of the physician (2). Was Osler referring to the demented elderly and institutionalized elderly, or to the community-residing elderly? Is death really a blessing to the elderly, or is it a dreaded adversary to be fought with the help of the physician and other members of the health team?

We have now developed knowledge and treatments that can cure or control the pneumonias and many of the other deadly illnesses of the heart, lungs, kidneys and blood. We are faced not only with more therapeutic options than Osler but with an enormously greater population of elderly. We are faced with an atmosphere of enthusiastic consumerism and litigation which push the physician toward treatment of all life-threatening illnesses. Perhaps most burdensome and difficult of all is the illness of senile dementia, characterized by many years of life without mental competence, and often accompanied by medical-surgical problems necessitating therapeutic decisions by patient, family, and physician. Thus, the physician is confronted with a high prevalence and a special category of ethical issues in his daily work with the elderly. In fact, it is likely that the impressive demographic and economic prominence of the elderly in our health system (3) has markedly contributed to the new emphasis on ethical issues in the practice of medicine with patients of all ages. Complicating the ethical issues are economic pressures. Clearly, there is no limitless supply of resources and thus choices will have to be made. But how, and by whom? Are we to apply criteria such as "a person's employability and so-called productivity?" Are we to be so concerned about "cost-effectiveness" that we make decisions "not to treat" based on such economic criteria?

A danger is at hand. We certainly must participate in making our limited resources do the most good. But any arbitrary social or psychologic criteria, such as age, intelligence, value or burden to society, will run the risk of leading to further criteria. It will also run the risk of placing the physician in the role of "cost saver" for society, rather than advocate and healer of the sick. As clinicians, we must remind ourselves and our communities that any increased need for auster-

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* Presented in part as a State-of-the-Art lecture at the 61st Annual Session of the American College of Physicians, April 21–24, 1980, New Orleans, Louisiana. Also accepted for publication in the *New York State Journal of Medicine*.

ity in the United States should be equally shared by various industries and sectors, and not fall disproportionately and illogically on health care.

The key issue affecting our clinical approach to elderly patients is the "value of human life." It has a quantitative aspect: is one day or year in the life of a 79-year old any less meaningful than a similar period in the life of a younger person? It has a qualitative aspect: do we have the right to view or the means to judge the quality of life of, for example, a demented patient residing in a nursing home as a "poor quality" and thus not worth sustaining?

Throughout our experience in the care of older patients in the office, the hospital, their own homes and in nursing homes, physicians are confronted with clinical issues that dramatically interface with ethical issues. The most prevalent of these issues will be highlighted.

Triage According to Age

We are now regularly asked to make choices in diagnosis and treatment that are cost-effective. We are asked to "triage" our cases, much as the officer and medic on the battlefield had to choose whom to treat and whom to let die. Age has become one criteria used by some in their "triage" efforts. Examples of "triage" situations include: 1) use of ICU beds, 2) admission from an emergency room to an acute hospital bed, 3) use of dialysis, and 4) use of consultants and other costly procedures.

Case Presentation

A 49-year-old male is brought to the emergency room with ventricular tachycardia following a myocardial infarction. All four beds in the cardiac intensive care unit are occupied by very sick, newly admitted elderly patients whose average age is 78. Should one older patient be moved out so that the younger patient can be admitted?

How are young house staff or experienced clinicians to deal with this rather typical dilemma? At times, an older patient is indeed moved out of the ICU in such a situation. As stated earlier, if we allow age to be used as a basis, we are opening the way to inequality and prejudice, and to additional criteria being applied such as intelligence, importance in society and economic status. The issue of a scarcity of medical resources has been highlighted by Fuchs (4) and Childress (5) by asking: "Who Shall Live?" I have already referred to the shortcomings of establishing criteria based on social values. An accompanying danger is that of choosing the decision makers: should they be physicians, clergy, lawyers, judges, family or committees?

Since logical arguments can be presented for all sides in triage situations, it is important that the physician remain the advocate for his patient and that each triage issue be discussed in an open fashion with decisions evolved individually for each patient.

There are those who believe that any triage system will inevitably be prejudiced against the elderly. For these skeptics, a system of allocation of lifesaving resources based on randomness and chance has been proposed by Childress for those of all ages (5). This system excludes biases and prejudices and presumes that all life is precious, "not to be categorized as more or less worthy."

As modified for the elderly, this is a two-step system. The first step is that of using medical criteria excluding age, such as arrhythmias, heart failure, cardiogenic shock and others. These criteria are applied to choose those who would benefit from the lifesaving treatment. In the second and final step, choices from this first group are made on a "first come, first served" basis or by the drawing of "lots."

I suggest that this is a fair and equalizing approach and deserving of further consideration, study and action.

Medical or Surgical Decision Making with the Mentally Impaired (Demented), Nonterminally Ill Elderly

Approximately four to eight percent (800,000 to 1,600,000) of the elderly U.S. population suffer from dementia with the figure increasing to 20 percent of those over 80 years of age. Who thinks for and speaks for these millions of persons? The physician is faced with an enormous dilemma in deciding about medical and surgical problems experienced by these patients. This is not the relatively uncommon, though much talked about terminal patient on a respirator, the Karen Ann Quinlan situation and the question of discontinuing life-sustaining treatment. Rather, it is the all too common dilemma of medical or surgical decision making with the mentally deteriorated patient who has the likelihood of many more years of life.

Case Presentation

A 78-year-old widow, active as a volunteer in community organizations, has experienced a progressive mental decline. She still drives a car but has had several recent accidents. Finally, she is placed in a nursing home. Shortly thereafter she is discovered to have carcinoma of the colon without apparent metastases. She is not capable of making an informed decision about surgery. Her family, very affectionate and involved, is comprised of a 58-year-old son and a 55-year-old daughter. The son states that his mother "would not want to live." He feels strongly that no surgery should be done. The daughter is more ambivalent and less certain of her mother's wishes. The case is discussed at the "team meeting."

Some of the medical students, residents and fellows are angry with the son and feel that this elderly woman should be allowed the statistically apparent benefit of surgery. The senior physicians, too, are mixed in their view of what was "right." One physician knew the patient for ten years.

At a team meeting many feelings are expressed, all focused on what is best for the patient. A decision is reached by the family—not to operate. Several months later the patient experiences intestinal obstruction. Another meeting with the family produces a decision for a colostomy to relieve the obstruction.

Who should have had the responsibility (and the authority) to make the original decision? What were the patient's wishes?

Questionable Legality of Family Role in Decision Making

Interestingly, it is not at all clear whether the adult children have a legal basis for decision-making power (6). Custom has allowed them the role of surrogate decision makers. This appears sensible in that family members seem to be the proper individuals to be responsible. Yet, often the story is different. The family may be emotionally or physically distant. Indeed, there may not be any close family members. This is more often the case for the aged widow, who may outlive her husband and children. There may be matters of inheritance influencing the family decisions, let alone obvious issues of affection and guilt.

The physician, too, will have multiple factors affecting his view: the known therapeutic value and the risks of surgery, the difficulty in dealing with a demented patient on a long-term basis, and the relationship with this particular patient or family.

The physician, too, has no legal right to make this decision for the patient. Traditionally the physician and family, with variable input from the patient, reach a decision, hopefully benevolent but sometimes desperate and after much soul searching. The physician who disagrees with the patient's family can withdraw from the case. However, this is not often done since there is an element of abandonment in this.

The Saikewicz Case and Decision Making by the Court

Recently, a decision of the Massachusetts courts (7) has renewed attention to this matter of the "incompetent" patient, so long a problem. Saikewicz is a 67-year-old, life-long mentally retarded and institutionalized man, uncommunicative, who developed acute myeloblastic, monocytic leukemia without pain. His physician wanted to treat the leukemia in the hope of prolonging his life a few months to perhaps over a year. His two sisters did not want to become involved. The hospital superintendant asked the probate court to appoint a guardian who then reviewed the matter and recommended against treatment. The probate court agreed with the recommendation and so ordered the hospital. The Supreme Judicial Court affirmed the order.

The logic was that the court felt that a competent adult has the right to refuse treatment for himself. Thus, a guardian for an incompetent adult could do the same for the incompetent. The court agreed with the current medical ethic, that "extraordinary means" should not be employed to prolong life when sensible therapeutic efforts have failed and the situation is hopeless.

The Karen Ann Quinlan case (In: Quinlan:70 N.J. 10, 355, A.2d 647, cert. denied, 429 U.S. 922 (1978)) was the first decision to allow a mentally incompetent adult to have a guardian (her father) make a decision to discontinue treatment, even if such discontinuance could result in the patient's death. The key point, in the New Jersey court's opinion, was the patient's constitutional right to privacy and thus to refuse treatment. This right was granted only if the patient's prognosis was poor and the patient would remain in a chronic vegetative state. Thus, without the court's involvement, the guardian (plus physician and committee) could make the decision not to treat. The court provided immunity from prosecution for all concerned.

But disagreeing with the New Jersey courts, in the Quinlan case, the Massachusetts court stated that the decision "not to treat" could not be made by a collaboration of family, physicians and hospital ethics committee (8, 9). Rather, the decision was too heavy for such and must be made only by the courts of law—that is, deciding both to treat and not to treat. The court also refused to equate the quality of a person's life (in the case of the institutionalized, mentally retarded person) with the value of life.

The Massachusetts courts have thus voted "no confidence" in the ability of physicians and families to act on behalf of the mentally incapable patient (10). However, many have pointed out that the courts are too slow to meet clinical needs; that the New Jersey-type decision making process by committees, physicians and family has safeguards in that it is open to court appeal by any of the parties involved; that the Massachusetts approach will lead to prolongation of treatment while the court tries to decide. The Massachusetts court was saying in effect that the matter of life (or death) is too large for any one person or one profession to decide. But to this author, the courts hardly seem an adequate substitute for family and physician.

The Dinnerstein Case: "No-Code" Orders and No Court Involvement

Subsequent to the Saikewicz decision, the Massachusetts Appeals Court decided "In the Matter of Shirley Dinnerstein" (1978, Mass. App. Adv. Sh. 736) that judicial approval was not required for a "no-code" order indicating that resuscitative procedures be withheld if the case was one of an irreversibly ill, terminal and mentally incompetent person. Dinnerstein was an elderly woman suffering from Alzheimer's disease; physicians intended to leave orders stating that no resuscitation procedures be employed if she developed cardiac or pulmonary arrest. The court said that the decision to classify a patient as "no-code" presents "a question peculiarly within the competence of the medical profession of what measures are appropriate to ease the imminent passing of an irreversibly, terminally ill patient in light of the patient's history and condition and the wishes of her family". While removing the courts from, at least, this one clinical situation, this decision did not fully clarify the role and rights of the immediate family (spouse, children, parents) to give consent for "no-code", yet appears to require the physician to obtain the consent of the immediate family or the patient's, legally appointed guardian.* This decision is not totally contrary to the court's decision in Saikewicz. Since Dinnerstein had no hope of even temporary improvement, there was no controversy, as there was in Saikewicz. Thus, the court emphasized that its involvement in discontinuing treatment was necessary only when controversy existed.

The Penultimate Will: A New Legal Instrument Akin to the Last Will, and Different from the Living Will, Allowing One to Choose One's Own Guardian and to State One's Wishes in the Case of Becoming Incompetent (11, 12)

As stated earlier, the most prevalent situation relevant to the uncommunicative patient and the need for medical decision making is not the dramatic case of the dying patient on the respirator but rather the very much alive, mentally incompetent and usually elderly individual, suffering from senile dementia and with the likelihood of many remaining years of life. Since most dementia patients cannot make an informed decision when presented with treatment alternatives and diagnosis, the responsibility falls upon the family and physician or the courts.

What has been missing is a knowledge of the patient's specific wishes, most importantly, his choice of surrogate or guardian (called "committee" in New York).

I have described in 1973 and 1975, with my colleague in the Law, R. Zicklin, a legal mechanism and instrument executed in the same manner as a last will, validating that while of sound mind and of any age, the individual chooses his guardian, addressing the painful though unlikely possibility of forthcoming incompetence (11, 12). It thus allows the individual, if he should become demented and with possibly many years of remaining life, an opportunity to "control" some of the events of his life, even during the period of dementia. We have called this instrument the "Penultimate" will. It declares (Table I) and specifies not only the individual's choice of guardian but also his wishes as to matters such as: 1) choice of physician, 2) choice of lawyer, 3) place of residence, 4) manner of handling available funds, and 5) other matters.

The designation of the guardian has the force of law in New York State, under Mental Hygiene Law 78.05. However, all of the other designations in paragraph 2, Table I (designation of physician, attorney, place of residence, use of assets), though not having the force of law, if thus known to the court, would be most persuasive upon the court in matters which the court might have to decide. California, too, has a law which provides an opportunity for an individual to draw up an instrument in the manner of the Penultimate Will.

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* *N. Engl. J. Med* 299:875–878, 1978.

TABLE I

*The Penultimate Will**

I, Richard P. Goodmind, residing at 700 East 72nd Street, City, County and State of New York, being upwards of 18 years of age and of sound mind, pursuant to §78.05 of the Mental Hygiene Law of the State of New York, or any similar or successor statute, do hereby make, publish and declare this to be my Last Designation of Committee† hereby revoking all other designations of persons to act as the commitee of my person and/or property heretofore made by me.

1. I hereby designate my brother, Philip R. Goodmind, who presently resides at 3200 Riverside Drive, New York, New York, as the person whom I desire to be appointed as the committee and both my person and property in the event that I shall be declared incompetent pursuant to Article 78 of the State of New York, or any similar or successor statute. If, for any reason, my said brother should fail or cease to act as such committee, then, in such event, I designate my friend, Edward Buddy, now residing at 1200 Riverside Drive, New York, New York, as the person whom I desire to be appointed as the committee of my person and property, in the place and stead of my said brother.

2. I hereby request that my said committee and any court which will have to make decisions with respect to my person and property in the event of my incompetence consider my following wishes:

(a) That Robert Doctor, M.D. be my physician whenever medical care or advice is needed;

(b) That my present attorney, Joseph Lawyer, Esq., who is familiar with all of my legal matters, be retained as the attorney for my committee.

(c) That if my wife, Susan Goodmind, agrees and my physical and mental condition permits, I prefer to reside in my present apartment and not in a hospital or nursing home; and I request my said committee to make whatever financial nursing and medical arrangements are necessary to accomplish this request.

(d) That if at any time of my incompetence, my said wife is deceased, I request that all of my assets be expended in keeping me as comfortable as possible during the remainder of my life and that no consideration be given to attempts to preserve my assets for my heirs.**

IN WITNESS WHEREOF, I have unto this, my Last Designation of Committee, set my hand and seal this 15th day of May, in the year Nineteen Hundred and Seventy-Four.

RICHARD P. GOODMIND ______________________ (L.S.)

SIGNED, SEALED, PUBLISHED AND DECLARED by Richard P. Goodmind as and for his Last Designation of Committee, in the presence of us and each of us, who at his request and in his presence of each other have hereunto subscribed our names as witnesses the day and year last above written; this clause having first been read to us and Richard P. Goodmind aloud and we having noted and hereby certifying that the matters herein described took place in fact and in the order stated. This Last Designation of Committee consists of three sheets (including this sheet), each of which bears the signature of Richard P. Goodmind.

______________________ Residing at ______________________

______________________ Residing at ______________________

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* §78.05 of the Mental Hygiene Law provides as follows:

"Designation of Person to act as committee in case of future incompetence

(a) Every person of the age of eighteen years or upwards and of sound mind may designate in writing a person or persons whom he desires to be appointed as the committee of his person, or as the committee of his property, or both, in the event that he shall be declared incompetent pursuant to this article.

(b) Such designation shall be executed and attested in the same manner in which a will shall be executed and attested, revoked, altered, or cancelled.

(c) The person or persons designated to act in the future as committee shall be disqualified from serving as a witness.

(d) If the court finds that the appointment of the person or persons so designated would serve the best interests and welfare of the incompetent, it shall appoint such person or persons as committee, in accordance with the designation."

† "Committee" is the phrase used in New York for Guardian.

** Neither the requests contained in paragraph "2" nor indeed any requests other than that for the designation of the desired committee have any force of law. However, it would be most persuasive on any court to know the desires of the incompetent in matters upon which the court might have to decide.

Recently this mechanism has been increasingly emphasized (13, 14) and it has been pointed out that Michigan is considering such a statute (13).

The Penultimate Will is a very different approach compared to the so-called "Living Will." The Living Will has focused on the issue of the "right to die" if "an incurable disease or injury occurs and treatment would only prolong the phase of dying." The individual requests cessation of life-sustaining treatments such as discontinuing a respirator (15, 16). Such legally-binding choice in advance, without knowledge of the specifics of the life and death situation, is open to grievous error and also may force the physician toward nontreatment in a case in which some uncertainty exists (13).

The Penultimate Will, by designating the guardian, allows one to have some "control" and input into the situation, while maintaining flexibility. It also goes far beyond the life-death precipice, to the many years of remaining life of the demented individual and to matters such as style of life, use of funds, and place of residence.

In the author's opinion, it would be advisable for all persons in middle or late life to draw up a Penultimate Will, just as more and more people have faced the issue of drawing up a last will. With the improved expectancy already accomplished, the Penultimate Will, now known to few, could become a potentially important means of continuing to influence one's own destiny.

The Mentally Clear, Alert Older Patients Right to Refuse Treatment, Including those Treatments which could be Lifesaving

It is not often that a mentally clear patient outright refuses treatment, particularly a lifesaving treatment. Though some may believe that this refusal becomes more prevalent with age, it is indeed unusual in late life. The older person cherishes each day of life as much or more than the younger individual. Yet there are instances when such refusal does occur. The courts have long established the competent individual's right to refuse treatment. The heated debate comes when the refusal is linked to life-preserving treatments such as insulin, digoxin, transfusion, surgery, or even so "simple" a matter as hospitalization. Physicians traditionally attempt to overcome these wishes of the patient and indeed seek out other approaches such as the possibility of a significant depression.

Case History

An 88-year-old man living alone at home, perfectly alert and apparently sound of mind, experienced recurrent severe congestive heart failure and pulmonary edema necessitating frequent hospitalizations. He received home care from our Geriatric Medical Program and specifically from a young resident physician and from the visiting nurse. Recently during a heart failure and pulmonary edema episode, he refused to be hospitalized again. After prolonged discussion the resident accepted, with ambivalence, the patient's decision to begin a plan of treatment at home. The visiting nurse feeling "unable to let him die needlessly," called an ambulance and had the frail, mentally sound individual taken to the hospital where treatment was effective, at least permitting improvement and a return home. The resident physician brought this matter to the attention of a health care team with a view toward planning for the next episode of pulmonary edema.

Some medical students felt that the patient certainly had the right to choose nonhospitalization. One student had made a house call along with the resident and was quite convinced that the patient was making a valid decision. Some experienced clinicians wondered if the patient was seriously depressed or incompetent in judgment. The resident physician was very uncertain as to what the "right" course of action is.

There are arguments for and against the legality and ethics of the patient's right to refuse crucial, lifesaving treatment and of the physician's participation in such nontreatment. The courts often tend toward the view that the individual has the right of self-determination, unless this individual is the parent of dependent minors. When the decision is made by clear minded patients, the situation requires the matching of courage on the part of the physician or team.

Passive Euthanasia with the Uncommunicative, Terminally Ill

Uncommunicative, terminally ill elderly patients frequently engender in the physician the conflict of discontinuing treatment and allowing natural events to occur. This is a fairly common, lonely, and soul searching situation for the physician. The question experienced by the physician is: do we relieve suffering by omitting treatments and allowing an earlier death? Or do we shorten life that wants to continue but cannot communicate this to us?

Here are poetic examples of two sides of this issue:

From the Notebook of Albert Camus, November 7, 1937 (17), character A.M.—an invalid—both legs amputated, paralyzed all down one side:

> "They help me when I want to relieve myself. They wash me. I'm practically deaf, but I would never do a thing to cut short a life in which I believe so strongly. I would accept even worse, blindness, deprivation of all my senses, loss of power of speech and of any contact with the external world—as long as I would feel within this dark, burning flame which is me and alive. And I should still give thanks for having let me continue to burn with it's flame."

From the Roman stoic philosopher, Seneca (18, 19):

> "Few have lasted through extreme old age to death without impairment, and many have lain inert . . . I shall not abandon old age, but if old age begins to shutter my mind, and to pull its various faculties to pieces, if it leaves me, not life but only the breath of life, then I shall rush out of a house that is crumbling and tottering."

For the physician, the decision to discontinue treatment is rarely felt as absolutely clear and correct. This is one of the heavy burdens of clinical medicine.

Responsibility to our Patients Who Enter a Nursing Home

When an older patient enters a nursing home, it is not unusual to have his medical care rendered by a physician other than his usual, primary physician. There is, in many of these shifts, an ethical issue relevant to the physician-patient relationship and the potential diminution in the quality of care. For example, the change of physicians may lend to:

1) inadequate transfer of information from one physician to another
2) breaking and restructuring the physician-patient relationship
3 loss of insight into clinical decision making because of the absence of subjective "impressions" gained during previous care of the patient.

Such cessation of involvement is a departure for physicians in the U.S., since we generally pride ourselves on being responsible for patient care in the community and in the hospital. Why not, too, in the nursing home?

The patient, physician, and the nursing home will benefit from continued involvement of the patient's primary care physician.

Nontreatment of Fever in the Nursing Home: A Modern Day Setting for Triage

A recent retrospective study of "nontreatment of fever in extended care facilities" in Seattle, Washington revealed that approximately 40 percent of patients with fevers were not treated (20). The mortality rate accompanying those fevers was 59 percent for the nontreated group and nine percent for those treated. The investigators concluded that physicians and nurses together reached intentional decisions not to treat in many of these patients and perhaps subconscious decisions in others. This finding confirms an impression long held, that physicians often actually make nontreatment decisions in life threatening illnesses in certain patients rather than prolong life at any cost.

Clinical experience suggests that it would be the patients with irreversible and extensively damaged brains who are often selected for nontreatment. Thus, it is surprising that neither dementia nor stroke showed "an important relationship" to nontreatment of fever. On the other hand, nontreatment decisions were related to factors such as excess nursing care needs and aloneness (patients without spouse). These factors, though apparently humane, run the risk of "ageism" linked to "nursing home-ism," a prejudice favoring non-treatment because the patient is old, alone, requires excess nursing care and resides in a nursing home.

Informed Consent: Clinical and Research Situations with Older Persons

It has long been a legal doctrine that each person has the right to determine when and if invasion of one's body will occur. This concept is highlighted in the doctrine of informed consent (21, 22), which states "that no medical procedure may be performed without a patient's consent, obtained after explanation of the nature of the treatment, substantial risks and alternative therapies." The exception to this is the emergency situation.

The doctrine received great notoriety in the early part of this century in relation to religious groups such as Jehovah's Witnesses and their refusal of blood transfusions for their adult and young children. The courts upheld the religious rights on nontreatment of the individual adult, but not when the adult was making such decisions for a minor.

Not only clinical therapies but also research efforts require the informed consent doctrine to be carefully followed. Research efforts are further scrutinized by institutional review committees to carry out governmental guidelines. The balance between protection of the individual and the improvement of the health of society through research is tenuous and must be constantly reevaluated (23).

This issue is well highlighted with elderly patients, both those in the community and those in hospitals and nursing homes. For the majority of the elderly who live in the community the issue of informed consent is not appreciably different from that of younger adults. The comprehension of the program, the purpose of tests and treatments and the potential yield may be clearly understood if the physician takes the time and clarifies all issues. At any age it may be difficult to obtain a truly informed consent. However, with the frail elderly and with the four to eight percent of the elderly who are demented, there are more likely to be cognitive problems compromising a truly informed consent. How, then, are we to proceed with certain diagnostic and therapeutic steps, let alone with research?

With regard to research, the problem is complex? Institutional committees may be reluctant to approve research projects with the elderly which they would tend to permit with younger adults. Though appearing quite humane at first glance, this policy may be a serious threat to progress in improving the later years.

The present day approach to these issues has been government rules and human subjects protection committees, which will not be as important, finally, as the responsibility assumed by each physician or researcher in the matter of obtaining truly informed consent from the patient and/or the surrogate.

The Physician's Responsibility in the Patient's Choice of Mode of Therapy and the Relationship of this Decision to Patient's Willingness to Take Risks

In choosing treatments, we may interpret the textbook version of patients as ageless and presume that what is appropriate for mid-life is appropriate for later life. Even if we acknowledge the biologic differences accompanying age, we may overlook the attitudinal changes that often accompany age. The attitude of 60-year-old patients toward a choice of therapy may be quite different from that of a 45-year-old. One recent study focused on presenting choices of radiation or surgery to patients of various ages who had cancer of the lung. Patients were informed about immediate and long-term risks and benefits. The long-term survival data presented to them favored the surgical approach (24). Yet the older patients chose radiation therapy. This may relate to the lesser immediate risk of mortality or pain from radiation therapy compared to operative mortality and/or pain, or to other, not yet obvious, age-related factors. Thus, the physician's approach to helping the patients choose between alternatives should be modified by awareness of the apparent preference for less risk taking or discomfort rather than longer life among older patients.

Excessive Surgery in the Elderly

There has long been a controversy about possible excessive surgery in the U.S., compared to Great Britain (26, 27).

Certain surgical procedures are becoming so frequent in the elderly as to merit discussion; for example, cataract extraction (27) and prostatectomy. The clinical and ethical issue is that with an aging population, one could present a case for operating on almost all older persons since so many have cataracts or prostatic enlargement with some urinary symptoms. Exact criteria are difficult to establish since so much involves the interpretation of function. We must avoid excessive surgery using the soundest and strictest clinical and ethical criteria in deciding upon treatment.

Communicating with the Older Patient about Serious Medical Problems

For all age groups of patients there is debate about "truth-telling" by the physician (28) when it comes to issues such as cancer and other fatal illnesses. Not to adequately inform the patient can lead to a dependence and an inability to choose and plan properly. This could establish a paternalistic relationship of patient to physician.

Some think that elderly persons do "not want to know" or "can't understand." In the absence of dementia, most older persons are perfectly capable of understanding the nature of the problem. Our own experience suggests that older persons indeed deal better with stressful life events and news of catastrophic illness than do younger persons.

This is not to say that "all" older patients should be told everything. Often, such information is best withheld from the patient. There is, as always, the need for individualized judgment and for the art of medicine.

Conclusions

The demographic changes, the economic difficulties, the medical-technical advances and the involvement of society in health care decisions and issues have combined to increasingly emphasize the need for consideration of the ethics of health care for those of all ages (29, 30) and for the particular issues affecting the elderly. The circumstances relevant to the elderly may prove the greatest test of our society's ethical values, judgments and strengths. The issue is finally the value of human life.

Addendum

The "Brother Fox" Case: New York Courts Involve Themselves in Decision Making

In the case of "Brother Fox" the New York court followed the Saikewicz Appellate decision of the Massachusetts Supreme Court in affirming the need for court involvement in decisions not to treat. Brother Fox was an 82-year-old priest in a clinically vegetative state and maintained alive on a respirator. His colleague, Reverend Eichner, was allowed, by the Appellate Division of the New York Supreme Court (Eichner v. Dillan, 73 A.D. 2D431, 416 NYS 2d517 (1980)), to act as committee (guardian), and to have the right to request the physicians to discontinue the respirator. In addition, Brother Fox had discussed the Quinlan case while he was mentally competent and expressed his desire not to be maintained on a respirator if he should become incompetent. The court gave great weight to this previously stated view of the patient, though did not make it a requirement in order to uphold a decision not to treat. Further, in Quinlan, but not Saikewicz, the court granted immunity to medical personnel if court procedures as outlined were followed (Brant, J. Last Rights: An Analysis of Refusal and Withholding of Treatment Cases. *Missouri Law Review* 46:337–370, 1981).

These decisions (Quinlan, Saikewicz, Dinnerstein and Eichner) represent the views of various state jurisdictions and lack consistency in their approach. The courts have not yet set out clear, consistent guidelines in the matter of incompetent patients and permission or refusal of treatment (Shaub, H. Z. The Right to Refuse Medical Treatment: Under What Circumstances Does It Exist? *Duquesne Law Review* 18:607-628, 1980, and Roth, A. B. and Wild, R. A. When the Patient Refuses Treatment: Some Observations and Proposals for Handling the Difficult Case. *St. Louis University Law Journal* 23:429–445, 1979).

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Aging, Diabetes, and Obesity: Standards of Normality

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There have been recent developments in two disorders which can be considered together. The theme that links them is a redefinition of the diagnostic standards for their diagnosis. Diabetes mellitus and obesity are common metabolic disorders and both have strong age components. From a diagnostic standpoint, they have certain similarities. In their overt forms, there is little problem in identifying them–no sophisticated diagnostic procedures are required. The decision concerning "cut-points" for the separation of normality from disease for both of these disorders is, however, necessarily quite arbitrary at this moment in medical knowledge.

Consider the tests in use. For diabetes, the glucose tolerance test is the standard procedure for the detection of the less-than-overt case; for obesity, certain anthropometric measures (usually only height, weight and sometimes an impressionistic judgment of body frame) are relied upon. In populations subjected to these tests, the results are "distributed"; that is, the results, when plotted, will in nearly all cases form the well-known bell-shaped distribution, albeit a bell that is asymmetrical. Thus, there is a gradual transition between the clearly normal and grossly abnormal state—a grey zone, if you will.

Decisions as to normality or abnormality should not be made solely on the basis of the distribution of values in a population. That is, the assignment of limits of normality based upon the mean ± 2 standard deviations will only separate subjects with unusually high or low values from those subjects who have more usual values. The definition of abnormality should instead be those values which are known to be associated with harmful or deleterious outcomes. Thus, depending upon the test, either the upper or lower tails of the distribution curve may be involved or both may be abnormal–and the tails may (accidentally) fall at the ±2 SD level but may not.

Let us return to the two specific examples at issue today. Standards in common use for interpreting the glucose tolerance test result in a rather small percentage of interpretations of abnormality—as long as the population being tested consists of healthy, young adults. Over the past 60 years or so, however, a constant stream of publications showed that this percentage became larger and larger as older subjects were tested, until by age 60 or so, some studies showed 50% or more abnormal tests–a decidedly uncomfortable percentage. The question that evolved from these studies was "to age adjust or not to age-adjust" and opinions were voiced on both sides (1-3). We came down on the side of adjusting and even constructed a nomogram from the data collected from the subjects of the Baltimore Longitudinal Study of Aging to permit the physician to rank individual test performances.

That proposal was, as we admitted, quite arbitrary, quite temporary, and expected to change as new information became available. This has now happened (4,5). Uncertainties remain, but at least an adjustment in diagnostic standards has been proposed which 1) has the imprimatur of all the major diabetes societies in the world and 2) has effectively removed from the classification of "diabetes" a very large fraction of the total population, especially the middle-aged and older segment of the population.

In one stroke (albeit a stroke which required several years of delicate diplomacy), literally millions of individuals have been removed from the diabetes category (or at least they would be in that category if they had been screened for diabetes by the glucose tolerance test). This public health achievement–the cure of millions of diabetics by the simple technique of reassignment–has its merry side. The achievement should, however, not be belittled. It took courage to face

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up to the task of changing the time-honored practices of generations of physicians, public health experts, and epidemiologists.

What was done? First, the exact technique for performing the test was clearly outlined. Second, a diagnostic flow-chart was created to deal with the classification of the confusing complexity of terminology associated with this diverse group of diseases—diseases which have in common an elevation of the blood sugar level. Third, the diagnostic standards for interpreting the test were clearly redefined. Today we can consider only the last of these achievements. The full report of the National Institutes of Health-National Diabetes Data Group (4) should be studied for further details.

The new proposed standards depend mainly upon the highest plasma glucose value on the 30-, 60-, or 90-minute sample and upon the two-hour level (Fig. 1). There is one cut-point at the intermediate time intervals and two cut-points at the two-hour interval. Thus, the standards can be represented as a triangle. The older standards were rather similar in that there was one cut-point at one hour and there were two at two hours. There were also two at the 90-minute interval but the standards still could be represented as a triangle. It is possible then for individual test results to fall either entirely above the triangle, entirely below the triangle, or to be intermediate. The relationship between the older and newer criteria can be appreciated by examining the figure.

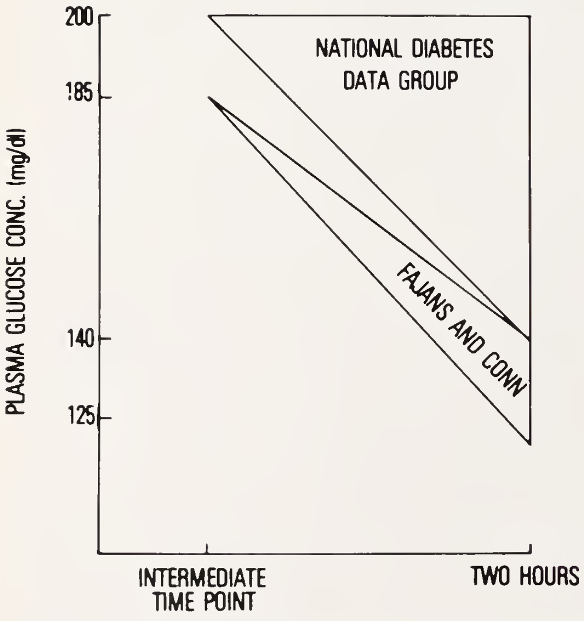

Fig. 1. Standards for interpreting the oral glucose tolerance test. The profound impact of the recent National Diabetes Data Group criteria can be appreciated from the large shift upward (toward higher glucose levels) in the cut-off points. A discussion of the older criteria can be found in West KM, Diagnostic Methods. In: Epidemiology of Diabetes and Its Vascular Lesions. Elsevier North-Holland, 67-126, 1978.

Since there are two possible results with the new criteria at the intermediate time point (either above or below 200 mg/dl) and there are three possibilities at two hours (at or above 200, 140–199, and below 140), six overall possibilities exist (Fig. 2). Incidentally, all of these results do occur when populations are tested. The "normal" and the "diabetic" categories are clear. Test results which show at least one value above 200 at the 30–90 minutes and with a value of 140–200 at two hours are to be classified as "Impaired Glucose Tolerance." (*Note:* The word "diabetes" is not to be applied.) The uncertainty as to the long-term prognosis of such subjects is emphasized by avoiding such prefixal modifiers of the term diabetes as chemical, subclinical, latent, borderline, asymptomic, pre-, etc.

There are a number of complexities in the diagnosis scheme that cannot be reviewed here, but one needs emphasis. A fasting value of 140 or greater that is confirmed is diagnostic. All glucose tolerance tests on such patients will be diabetic; therefore, the test should not be done. Or, if the classical symptoms of diabetes are present, then even a single plasma glucose value that is unequivocally elevated is diagnostic.

It should also be appreciated that the glucose tolerance test has relatively poor reproducibility; therefore, even a diabetic test result requires a confirmatory second test before the disease label should be affixed. Similarly, a test result of "im-

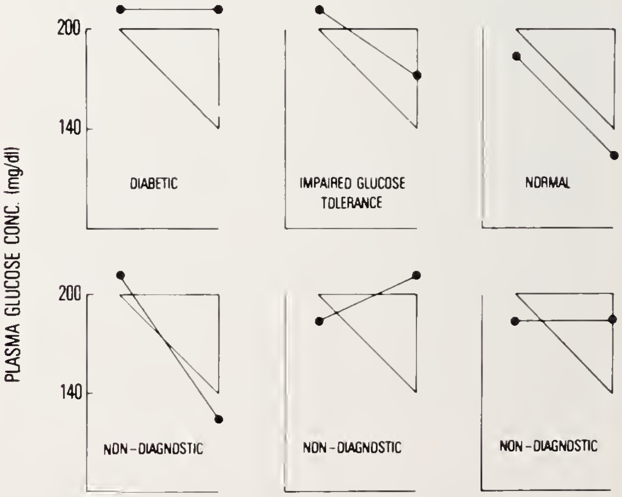

Fig. 2. Six types of results of glucose tolerance testing by the National Diabetes Data Group criteria. See Figure 1 for the actual cut-off points which define the diagnostic triangle.

paired" calls for follow-up testing and even the three varieties of nondiagnostic test results should be followed-up.

Furthermore, there is evidence that fasting values in the 125−139 range rarely occur in normal people and, in fact, even the 115−124 range is unusual enough that these individuals should also receive repeated fasting glucose analyses at a minimum.

There is no question that in the absence of a truly definitive marker for diabetes, the glucose tolerance test will continue to be used. Certainly, the test will be employed as a tool in both epidemiologic and clinical research. The question is, under what circumstances should it be used in clinical practice? A number of situations have been suggested as indications for testing:

1. Certain subjects are known to be at high risk for the development of diabetes. Periodic testing of these individuals should be considered:
   a. Gross obesity.
   b. Mothers of infants weighing more than nine pounds at birth.
   c. Women with poor pregnancy history (multiple spontaneous abortions or infants with birth defects).
   d. Certain racial-ethnic groups with high prevalence of diabetes.
   e. Relatives with certain HLA haplotypes or insulin antibodies.
2. Subjects who have previously been found to have abnormal or questionably abnormal fasting or random plasma glucose values or glucose tolerance tests.
3. Subjects with unexplained glycosuria.
4. Patients with symptoms, signs, laboratory findings, or illnesses known to be highly associated with diabetes. Examples are:
   a. The classic triad of polyuria, polydipsis, and polyphasia.
   b. Recurrent infections.
   c. Hyperlipidemia.
   d. Neuropathy, retinopathy, peripheral occlusive vascular disease, coronary heart disease.

Finally, it is necessary to stress that even the recommendations of the National Diabetes Data Group (NDDG) can be expected to be modified as more laboratory and epidemiologic evidence become available. We may very well need to become somewhat more sophisticated in the way we interpret laboratory tests. Medicine is simple as long as we have values given to us which clearly classify individuals into distinct diagnostic categories. Suppose though that, in fact, tests results do not place individuals into diagnostic boxes—that a test result has to be interpreted as indicating a certain statistical likelihood of a disease developing at some future date. We need to know those odds, the probable error in those odds, and how to convey such complex interpretations to our patients. Accurate information on such questions are beginning to be available but are not yet definitive.

The NDDG report reviews a number of prospective studies of populations who have received the glucose tolerance test and who have been followed long enough for some conclusions to be drawn. In fact, those conclusions were instrumental in the decision-making for the Report. In the same month that the Report was published, an important collaborative study also appeared−the International Collaborative Group (5). The fifteen populations of men generally in the 40−59 year age range came from the United States, Great Britain, Ireland, Finland, Switzerland, France, Denmark, Italy, Australia, and Japan. The basic design of the study was to measure glucose tolerance (and other risk factors) at entry and to follow the subjects for the development of coronary heart disease and mortality.

Four of the studies have not yet reported their follow-up results. Of the remaining 11, one performed fasting levels only and one reported only a random blood glucose analysis. Therefore, nine studies reported their results with reference to either a one-hour or two-hour glucose tolerance test (and one study reported both time periods). All of these divided their subjects into quintiles of glucose tolerance. Thus, the level of glucose associated with poor outcomes (coronary disease or death) could be determined. While known diabetics were eliminated from the study, inevitably some diabetics were detected by the initial test.

Thus, there was a range of glucose values for each study for the worst 20% of the population. The lowest values in this range were 120 to 194 in the five studies which reported one-hour glucoses to highest values of 421 to 564 mg/dl. In the five studies which reported two-hour values, the lowest values in their top quintiles ranged from 97 to 140 and the highest values were 368 to 580 mg/dl. The unfortunate point to be made is that it is not possible from these studies to test the long-term significance of the "Impaired Glucose Tolerance" category, a group which at two hours ranges from 140 to 200 mg/dl and which also had to exceed 200 mg/dl at an intermediate time point. The fact is that the range of glucose values included in the upper quintile ranged both far below to far above the "Impaired" category.

Despite the fact that some clearly diabetic subjects were included in the top quintile category, there still was a lack of uniformity in the outcomes. The overall conclusions of the report pertinent to this paper were:

1. The results do not indicate an association between asymptomatic hyperglycemia and coronary heart disease that is consistent, strong, and graded.
2. The results do not consistently show evidence for a threshold relationship.

Thus, within the limits of similarity between "asymptomatic hyperglycemia" and "impaired glucose tolerance," these grey areas of performance are just that—neither black nor white.

Let us turn now to the other area in which our ideas of normality are beginning to shift—obesity. The similarities to diabetes are striking. First, the test in common use to identify the presence of the disorder is rather crude. Height-weight tables can only indicate the degree that the subject is overweight (not necessarily obese) in comparison to standards of "desirability" of uncertain quality.

Secondly, changes in fatness with age are characteristic of populations in developed societies, just as glucose levels tend to increase with age.

Thirdly, there are gross examples of both disorders which everyone can agree on, but there is a large grey zone of intermediate levels of unknown prognostic significance. Furthermore, there are obvious links between the two disorders; the noninsulin-dependent variant of diabetes is much more likely to develop in obese than in lean individuals.

Fourthly, both disorders are associated (at least in their overt stages) not only with high mortality but, also, specifically with a higher rate of development of coronary heart disease and with other dangerous associations such as hyperlipidemia and hypertension.

Perhaps the major difference between the two—in terms of giving practical advice to physicians, to public health officials, to researchers, and, indeed, to the public itself—is that there has not been a "National Obesity Data Group" assembled to wrestle with a *modus vivendi* for dealing with obesity.

Yet there is, if anything, even more information about the long-term hazards of obesity than there has been about diabetes. The reasons for this are probably two-fold: 1) it certainly is easier to measure height and weight (indeed, some studies simply ask the question!) than it is to perform even a simplified glucose tolerance test, and 2) we are in the custom of considering that some enormous fraction of the adult population of developed societies are dangerously obese (perhaps over 50%) while public health statistics are cited to indicate that only some 2% of the overall adult population is diabetic—perhaps ranging from less than 1% in the early adult years to some 6% in the later years.

Over 40 populations have now been studied with respect to the impact of overweight on total mortality. These are studies which, in design, are similar to those noted in the discussion of the International Collaborative Group (5), above. In fact, some of the data on the effects of overweight come from those reports. In addition to these reports, there is a truly vast literature on other harmful associations of obesity, ably summarized by Bray (6).

In this discussion, however, we limit ourselves to the obesity-mortality association. The number of citable studies which offer data on this link depends upon the criteria of acceptability. The quality of the studies range from the trivial to the not-quite-sublime. Problems are rife: 1) The technique for selection of the population sample, 2) the quality of assessment of obesity, 3) the short duration of follow-up, 4) the incompleteness of follow-up procedures, 5) the technique of computation of mortality rate, and 6) the inadequate size of the population sample. There are problems not only in experimental design but, also, in the details of reporting the results.

Still, the very diversity of the styles of experimental design adds some strength to the conclusions that can be drawn, since some facts emerge clearly.

The accurate measurement of obesity (that is, the fraction of the body occupied by fat) is performed with difficulty. Various laboratory techniques have been described (7) but the more accurate ones are not suitable for large scale population samples. Thus, reliance is placed on measurement of height and weight (and, in a few cases, of weight alone!). Several studies have estimated subcutaneous fat by the skinfold technique and one by roentgenography. Those that have relied upon height and weight have subsequently combined these two measurements into a single number: 1) by a formula which "corrects" for height such as the Body Mass Index (wt/ht^2) or similar formulations or 2) by computing a relative weight for height. The second technique requires the use of a height-weight reference table. The tables in common use are the 1959 Desirable Weight Tables for men and women (8). In these tables, a splay of weights is provided for each inch of height dependent upon body frame. The decision as to which of three body frames the individual subject belongs (Large, Medium, or Small) is left to one's discretion. In any event, the technique always used (apparently) is to select the middle of the medium frame for the specified height and sex as the single reference weight. The computation of a "relative weight" or an "obesity index" is then easily made: the subject's actual weight divided by the reference weight.

In some studies, the individual's weight is compared to the mean weights per height of the age and sex category of that same population. In other studies, other reference populations are used. One important study, for example, used an insurance table of 1912 as a reference.

To compare studies using these diverse techniques, I have recalculated the data to the standards of the 1959 Tables. The advantage of this (aside from providing the needed uniformity) is that most physicians and researchers have some tangible concept of the meaning of "20% overweight" but would find results reported as a Body Mass Index of 26.5 kg/m^2 quite uninterpretable.

As a matter of fact, the interconversion of "Metropolitan Relative Weight" to Body Mass Index is quite simple. For men, a relative weight of 1.00 is equivalent to a body mass index of 22.1; in women, the constant is 21.2. The derivations of these constants were made from the Metropolitan 1959 table unmodified for men despite the fact that insured men were measured with shoes (assume a one inch heel) and with indoor clothing (assume about 4–5 pounds including shoes). It happens that the increase in weight per inch of height in the 1959 table is very close to the weight of clothes. Therefore, a table based upon height with shoes and weight with clothes is applicable without adjustment for nude height and weight for men.

For women, however, we are told that the average heel height was two inches in the epoch of the 1959 insurance report. Therefore, a one-inch height adjustment nicely corrects for the approximate weight of women's clothing—but the one inch adjustment in height must be made before deriving the 21.2 constant noted above.

It is remarkable that prior to 1960 only the insurance industry tackled the question of obesity as related to survival. The Society of Actuaries and the Association of Life Insurance Medical Directors of America have, since the turn of the century, periodically analyzed their mortality data and have reported them in detail. Their most recent report has just been published (9). Even in the 1960's only three studies were published. By the 1970's, reports began to appear in profusion. They are still so recent that their cumulative impact on diagnostic standards have not yet been felt. Nearly half of the populations are in various parts of the United States. The rest are from 11 European countries, Australia, and Japan.

I can here review only several of the major studies. Fifteen (15) of the studies were reviewed in a previous publication (10) and I will not repeat those results here. Several studies have subsequently been published. The Seven Countries Study under Ancel Keys' direction is a remarkable achievement (11). The countries are the United States, Finland, the Netherlands, Italy, Greece, Yugoslavia (Croatia and Serbia are separately reported), and Japan. The mortality data are presented by quintiles of relative weight. The cut-points of the quintiles are available in the Appendix and Keys' relative weight can be readily converted into "Metropolitan Relative Weight" equivalent. The results show that in seven of the eight populations, minimal mortality occurred at a relative weight greater than 1.00. Furthermore, in all of those seven, the highest mortality occurred in the leanest quintile of these diverse populations. In Japan, Croatia, and Serbia, minimal mortality occurred in the most obese quintile—in the Yugoslavians this represented those individuals who were at least 15%–20% over desirable weight. The Japanese as a whole are much lighter than the other populations, so that the most obese quintile still represents subjects who were some 5% and more over desirable weight.

In two of the countries, the U.S. and Greece, minimal mortality occurred in the next to most obese quintile. In the U.S., this included subjects some 15% to 25% over desirable and in Greece some 5% to 15% over desirable.

In two further countries, Italy and Finland, the mid-quintile, that is, the third quintile, showed minimal mortality. This represents subjects some 10% to 20% over desirable in Italy and some 5% to 10% over in Finland.

The single example of the eight in which leanest was lowest was the Netherlands. But here there was essentially no difference in mortality among the third, fourth, and fifth quintiles—no increase in mortality was seen until weights some 10% over desirable occurred.

An important study under the sponsorship of the American Cancer Society was recently published (12). The study is unique in that it was conducted by 68,000 volunteer workers on a population of 750,000 men and women in 26 states followed for about a 12-year period. Unfortunately, heights and weights were obtained by a questionnaire; actual measurements were not made. Thus, the subjects, and especially the women, are reported to be very much lighter than those of the general U.S. population (13). This may partly reflect sampling for generally higher socio-economic class women than the general population (as they noted) and may partly reflect the tendency to report heights somewhat higher and weights somewhat lower than the true values. Nevertheless, the results are certainly worth examining. The report presents mortality ratios for obesity classes based upon the average weights of the sampled population. The average weights of men from age 30 to 70 were about 14%–16% greater than the 1959 desirable weight and the average weight of the women increased from about 8% greater than the desirable weight in the younger women up to some 18% greater by age 70. Thus, the Weight Index category of 090–109 (those subjects within 10% of their *average* weight) actually are as much as 104 to 126 above desirable for middle-aged men and 106–131 above desirable for middle-aged women. The minimal mortality for men in each age decade from 30–39 to 80–89 years occurred at their average weight, that is, distinctly above desirable weight. Minimal weight for women was usually in their 080–089 category (or essentially at the desirable weight for middle-aged women). Interestingly, the 80–89 year old men and women who survived best were distinctly on the obese side although there was, in fact, very little difference across the obesity span. Another feature of the study worthy of note is that the leanest group (those who were 20% or more below their average) had high mortality rates, despite an initial screening procedure to rule out subjects known to be ill. Especially in the oldest age groups, those in the 70's and 80's, underweight carried a distinctly unfavorable prognosis; it was better to be quite grossly obese than to be in the lowest weight group.

Another interesting report came from the "Pooling Project" (14). Among these five populations, Framingham and the Chicago Peoples Gas Company have reported their data in detail elsewhere and were included in a previous summary (10). Three other populations reported their obesity-mortality data in the pooled report: the Chicago Western Electric Co., the Tecumseh Study, and the Albany Study. The data are reported only according to the mean relative weights at the initiation of the study of those subjects destined to die in the 12-year follow-up period and of those subjects destined to survive. The results for these three populations are:

	Mean Relative Weight		
Population	Deaths	Survivors	Deaths/ Survivors
Chicago WE Co.	117.6	115.1	1.02
Tecumseh	118.8	119.1	1.00
Albany	112.1	114.3	0.98

Thus, obesity judged this way, was not predictive of a higher mortality rate. Note the high mean relative weights in all groups—from 12% to 19% over desirable weight. Thus, these populations were on the average distinctly over the desirable weight level. If a graded deleterious effect of obesity were expected over the desirable weight, then those destined to die should have been considerably more obese than those destined to live. The fact that the two groups (in all three studies) had nearly identical degrees of obesity on the average is compatible with a U-shaped relationship of obesity to mortality with the nadir of the U at the *mean* weight, that is, some 12% to 19% over the desirable weight. It would be worthwhile having a breakdown, say, by quintiles of obesity rather than a report by mean obesity level only.

Ancel Keys has reported an additional population group by the same technique recently, the Minnesota Businessmen's Study (15). The mean Body Mass Index of the deaths after a 30-year follow-up of men studied at age 45–55 years was 25.1 as compared to a BMI for the survivors of 24.8. Thus, the relative weights of these two groups averaged about 1.137 and 1.120, only a 1.5% difference. Again, this is compatible with a U-shaped curve with the nadir near the average weight.

A number of points should be made. This analysis of the literature on obesity is, in one sense, very limited since only total mortality has been considered. There is more to life than mere survival; on the other hand, there is nothing to life without survival. Experience with epidemiologic studies has taught us that it can be dangerous to focus exclusively on coronary heart disease as an end-point. Consider the studies of dietary intervention for coronary disease and the trial of diabetes therapy (oral agents vs insulin vs placebo). In a well-known diet study, coronary deaths tended to decrease while total mortality remained unchanged; in the second instance, coronary deaths increased while, again, total mortality was unchanged.

Thus, specific causes of death must be examined in relation to obesity. But, even after this is done, total mortality will still be the summarizing end-point. It is worth examining. Since (by definition) there will be more total deaths than deaths attributable to CHD, the cancers, cerebrovascular disease, pneumonia, and influenza, etc., there is greater statistical comfort in the larger N's produced in total mortality analyses.

Still, the literature on obesity and CHD is however very extensive and is filled with controversy. This topic is, however, beyond the scope of this paper. Data on obesity and the cancers is not as extensive and there is also generally a lack of consensus in most areas. Consistent, convincing results are evident for two of the specific carcinoma sites: uterine carcinoma is associated with obesity while bronchogenic carcinoma is associated with leanness.

This latter association is almost certainly attributable to the fact that cigarette smokers are quite consistently somewhat leaner than nonsmokers. Thus, the apparently harmful effects of leanness for this cause of death is confounded by the smoking-leanness association. Could such a link explain the surprising shift of the minimal *total* mortality point toward obese subjects? It is unlikely in view of the several studies which have carried out the necessary analysis to examine the obesity and total mortality association separately in smokers and nonsmokers (16–18).

We are left with the conclusion from the analysis of many studies that minimal mortality does not occur in the leanest fractions of developed populations. In fact, the overall impression one gets is that there may well be quite a broad range of weights associated with relatively low mortality and that this range extends from perhaps the upper half of the total range in the 1959 desirable weight tables to a level perhaps as much as 20 or even 30% above the middle of that range.

There are so many well-known deleterious effects of even rather moderate obesity that the overall mortality results appear contradictory. It appears that the effects of adiposity are complex. Known harmful effects seem to be balanced by largely unknown beneficial effects on survival. Some speculations on what these might be as well as on the possibility of hidden artefacts in the numerous studies have been previously considered (10).

In summary, in two related areas, diabetes and obesity, standards to define the normal state either have been or soon will be modified considerably. The impact on individuals in the population, on public health, and on the practice of medicine can be far-reaching. The intellectual effort to define normality and the results of studies designed to meet that goal have raised many additional questions which only future research will resolve.

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Cancer in the Aged

James F. Holland, M.D.

The concept that cancer is worse than all other diseases among the aging, is not tenable in all its constructs. Some cancers are curable. Our target must be cures for the rest, until prevention is achieved.

Cancers constitute a particular challenge for aging, because we are talking about two populations of cells, the population of the host and the population of the tumor. By definition, the population of tumor is of an age different from the population of the host. The age of the tumor makes a huge difference in its behavior, in the way it grows, and in its susceptibility to therapy.

Figure 1 shows a classic experiment of Abraham Goldin of the National Cancer Institute (1). In the left panel are leukemias five days after transplantation in mice. In the right panel, the tumors are nine days posttransplantation. Survival of the treated animals is shown on the ordinate vs the dose of drug given on the abscissa. A major difference appears upon treating the young and the old tumor. Not only is overall therapeutic result different, but a difference is evident in the schedules of treatment. A single treatment every fourth day is optimal in the young tumor, but this effect is completely obliterated in the old tumor. A whole spectrum of aging phenomena in the tumor itself imparts differences independent of the age of the host animal, these involve tumor size with its influence on adequacy of oxygenation and nutrition, and growth kinetics. Based upon this classic experiment in mice, intermittent dosing with the same drug, methotrexate, was adopted for treatment of acute leukemia of children compared to conventional daily treatment. An exact replication of the findings were found in children: no difference in results dependent on drug schedule in advanced disease, but dramatic superiority of the intermittent methotrexate schedule when the leukemia had been reduced to a low body burden, or early tumor, by drugs used for induction. Some of the first cures that were achieved in leukemia resulted from changes in methotrexate schedules. It became obvious also that if one could, in effect, change the age of the tumor by doing something that would take the equivalent of a 9-day-old tumor and reduce it in size to that of a 5-day tumor, (induction chemotherapy) one might be able to alter therapeutic effectiveness. Until this experiment was done, all children who were treated with methotrexate were treated with the antimetabolite when they presented with a symptomatic large tumor, equivalent to Goldin's mouse tumor of advanced age. We began to use an induction treatment with vincristine and prednisone, returning the large tumor to a small one, from the equivalent of an aged to younger tumor. This led to a high level of curability. Thus, we must pay consideration to the age of the tumor as well as to the host.

Dr. Alexander Sun at Mount Sinai has found a major difference in the aging of tumor cells and of normal cells that may constitute a fundamental understanding of differences between the two fields. Normal cells have a finite life span in cell culture, being limited to about 30 to 50 doublings, after which the culture will no longer propagate. Cancer cells have an infinite life span in culture. They have lost the mechanism of aging. What Dr. Sun has shown is that as the population doublings increased in the normal cell line WI38, a substantial increase occurred in a specific enzymatic activity, in the cell membrane, 5′-nucleotidase. He demonstrated this increase with aging to be true for several normal cell lines. This opens up a biochemical definition of aging. It then became important to look at cells that didn't age in culture. Eleven lines of human cancer cells growing in culture, many of them isolated by Ohnuma (Mount Sinai) showed no increase at all in their 5′-nucleotidase in successive generations. Dr. Sun has also discovered that the abnormal cell lacks this activity to hydrolyze 5′-nucleotides not because the enzyme is absent, but because in the cancer cell there is an inhibitor of enzyme activity. A homogenate of cancer cells mixed with normal cell homogenate caused marked reduction in the normal 5′-nucleotidase activity. This

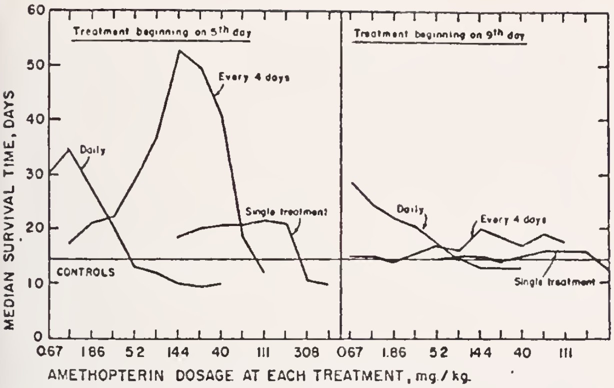

FIG. 1. Survival of mice with leukemia L1210 is altered by the dose schedule of methotrexate, and by the size of the tumor on day 5 and day 9. The principle that intermittency of drug dosing is superior in biologically early tumor, but not in late tumor in which no difference between schedules is seen, has been validated in acute lymphocytic leukemia of children.

suggests a whole new biochemical approach that merges the field of aging and of cancer. It may give new leads in understanding some of the differences between cancer cells (immortal and perpetually young) and the aging of normal cells. We need to relate the mechanisms of why this enzyme is at the cell surface and why its absence is apparently associated with an infinite life span of cancer cells.

One of the touchstones of chemotherapy is how to approach tumors in order to kill them with the absolute necessity of allowing the patient to survive. Survival curves for children with acute lymphocytic leukemia are shown in Figure 2. When the use of chemotherapy first began as a research undertaking we were unsuccessful. In 1956, no child lived more than two years. By successively adopting new information, the Cancer and Leukemia Group B, which I have had the privilege to serve as Chairman, began an upward progression so that now approximately 50% of children with acute lymphocytic leukemia are cured. Additional information derived in other cancers has been significantly influenced by the strategy developed in acute lumphocytic leukemia. In acute myelocytic leukemia, which occurs predominantly in adults, we are some ten years behind the progress in children, since the first curve starts ten years later when essentially no adult was then cured of leukemia. The data are improving, a number of patients are alive and well without evidence of disease six to eight years later after chemotherapy or chemoimmunotherapy of acute myelocytic leukemia, and some survival curves are very close to a flat, albeit low, plateau (Fig. 3).

An important clinical phenomenon in this

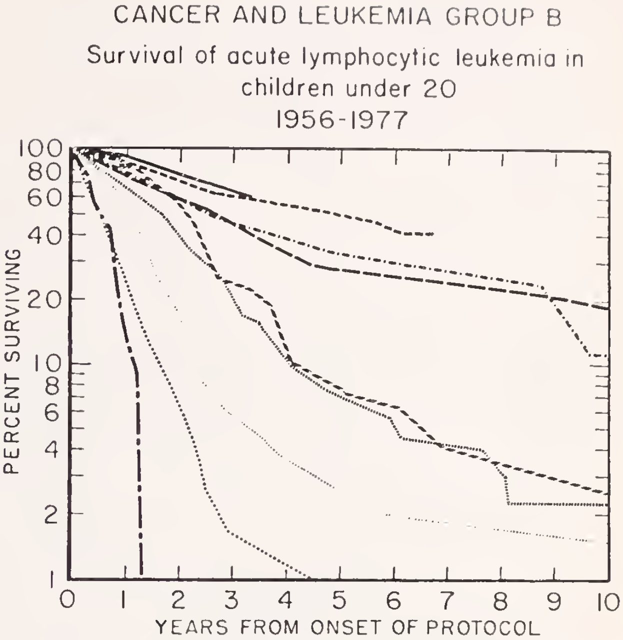

FIG. 2. Successive studies in the treatment of acute-lymphocytic leukemia making use of prior data to design subsequent therapeutic regimens. Stepwise improvements indicate more children entering complete remission and remaining there longer. Because the graph is plotted semilogarithmically, approaches to the horizontal indicate a slower relapse rate, and large proportions of the population several years after initiation of treatment are apparently disease free.

leukemia relates to aging as we ordinarily think of it. Three treatment regimens were studied in acute myelocytic leukemia by Yates et al (3). All patients received seven days of cytosine arabinoside by infusion and were treated identically except for the drug that constituted the second component of their combination chemotherapy. One group received adriamycin 90 mg/M^2, another received the standard treatment, daunorubicin 135 mg/M^2. Adriamycin and daunorubicin are extremely close chemical analogs of one another; the only difference is a hydroxyl group substituted for a hydrogen atom. Because the primary comparison was being made at two different dose levels (based on two separate sources of antecedent clinical experience) the dose of daunorubicin in a third arm was also reduced to 90 mg/M^2 to make it equimolar to adriamycin. When patients with acute myelocytic leukemia were anlyzed by age for successful induction or remission, it was found to be inversely related. Some 80% of patients below the age of 20, but only 15% above the age of 70 reached complete remission. Mortality during induction is high, not only because unremittent acute myelocytic leukemia is a lethal disease, but because the treatment causes damage to the bone marrow. Treatment

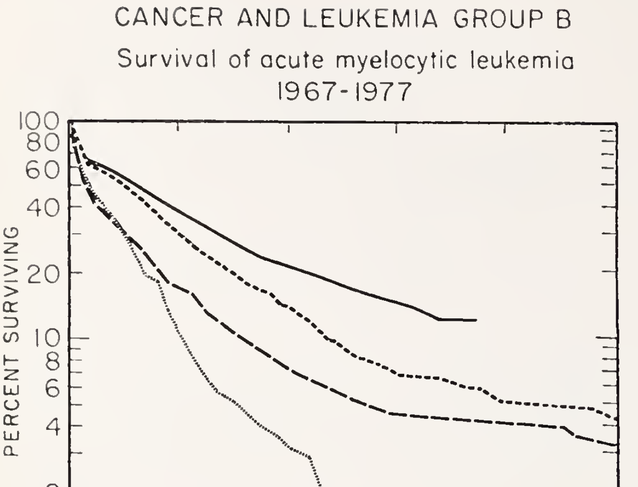

FIG. 3. Survival of patients with acute myelocytic leukemia shows improvement in a fashion reminiscent of acute lymphocytic leukemia in its early stages of chemotherapeutic control. Most of these regimens use cytosine arabinoside and daunorubicin as induction treatment and a variety of maintenance programs.

leads to a period of iatrogenic marrow aplasia during which infection and hemorrhage are common. The reason for the increasing failure to reach remission with advancing age is a very rapidly augmenting mortality. Patients die early from uncontrolled leukemia or more commonly from marrow injury from the treatment. Not much difference separated the adriamycin 90 from the daunorubicin 135. Adriamycin, the experimental agent, was not significantly better than the standard treatment. But happily the design included the low dose daunorubicin, 90 mg/M2. Although this was found to be less effective in the young than daunorubicin 135 mg/M2, in patients over the age of 60 a substantial increase in remission induction and a decrease in the mortality occurred on daunorubicin 90 mg/M^2. Thus the preferred dose of a drug in a specific disease may relate to the age of a subject; there are influences attributable to the age of the individual and to the age of the tumor involved. The age of the individual influences his ability to sustain chemical trauma of powerful cytotoxic drugs to his marrow, liver, kidneys and gut. The age of the subject studied may therefore influence therapeutic outcome. This phenomenon is sometimes noted in differences that exist in reports from referral centers and experience in physicians' offices. All referral institutions may be obliged, because of limited resources, to select patients. When they do select patients, they often choose the young rather than the old. Published reports of truly remarkable treatments are often better than subsequent general experience because they are made on patients disproportionately younger than those affected in the general population.

Cancers can be described in terms of the numbers of cells they contain. A tumor with 1,000 cells would be a kilocytoma, one with 1,000,000 cells a megacytoma. The volumes of these tumors are very small indeed, a megacytoma approximating a cubic millimeter. It is not until 1,000,000,000 cells exist, a gigacytoma, that a tumor reaches a cubic centimeter, the ordinary absolute minimum threshold for clinical detection. For most of its life span, a cancer is below the level of clinical detection. Cure of a gigacytoma is the cure of a very advanced tumor. Tumors don't grow from 1,000 to 1,000,000 to 1,000,000,000 cells. Rather at their most rapid pace, they grow from 1,000 to 2,000 to 4,000 to 8,000 cells by doubling. Furthermore, every tumor cell that doubles doesn't necessarily endow the two progeny with the capacity both to double; some newly divided cancer cells may mature imperfectly without further multiplication. In addition, every new cell may not survive; cell death may occur from vascular accident, nutritional deficiency or uncertain cause. A concept emerges that a palpable cancer

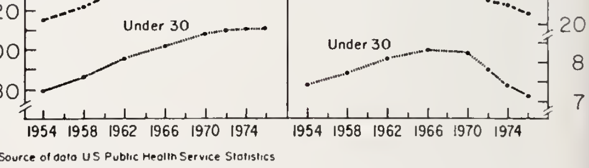

FIG. 4. As the population in the United States increases by age cohorts, the number of cancer deaths does not. Beginning in the late 1960's the number of deaths from cancers under the age of 30 has sharply decreased. The number of cancer deaths under the age of 45 has decreased, and the number of cancer deaths under the age of 60 has plateaued. Improved survival from acute lymphocytic leukemia, Hodgkin's disease, testicular cancer, sarcomas of children, lymphomas and other neoplasms account for most of the changes.

is a very old tumor indeed, a gigacytoma. "Solid tumors" aren't solid; gigacytoma is a much more meaningful term. Gigacytosis is the dissemination of 1,000,000,000 cells around the body. Even though these can't ordinarily be found anatomically because the metastatic islands are too small to be clinically detected, they exist at a most critical time therapeutically. Gigacytosis is kinetically young despite the age of the host or the original tumor. Surgery for the original tumor has the effect of leaving only a low density population as metastatic gigacytosis, a kinetically younger tumor which appears to be more susceptible to chemotherapy (2).

Cancer chemotherapy works. The population of the United States has grown older. But cancer deaths under the age of 45 do not parallel the population increase in that age bracket. Indeed, despite the population increase the total number of deaths has declined. There is a major decrease below the age of 30, attributable to less deaths from acute lymphocytic leukemia, Wilms' tumor, osteosarcoma, Hodgkin's disease, testicular cancer and others. The trend of mortality decrease began between 1966 and 1970. This was the background on which the National Cancer Program was founded. Below the age of 45 cancer deaths have decreased. Indeed, for all individuals in the United States under the age of 60, the number of cancer deaths per year has plateaued despite a continuing climb in the population.

It is my belief that as we take the advances in understanding that have been made and extend them to the entire medical community, even in the aged we will begin to see a decrease in cancer death rates. Furthermore, all physicians and health professionals should recognize that if it weren't for the cigarette, our total cancer mortality would already be declining sharply, because the only category of cancers that are increasing significantly in mortality are those directly attributable to cigarette smoking.

Cancers are potentially curable diseases. They are actually curable in many situations by the use of surgery, radiotherapy and chemotherapy alone or in combination. By advances in understanding why cancer cells behave the way they do, we may come closer to final answers quicker than we have ever dared to hope.

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Biobehavioral Approaches to Dementia

Carl Eisdorfer, Ph.D., M.D.

One of the problems in the field of aging, indeed a problem in all of medicine, is that of nomenclature. I would like to start with a focus on the term senility.

Unfortunately, some people have stopped there with rather serious consequences. The notion of senility implies two things, neither of which is valid. It implies, first of all, the inevitability of profound cognitive decline with age, this is simply not true. We are told that humans have a choice between death and senility, the assumption being if we live long enough, we will become senile.

Senility is not inevitable. About ten to fifteen percent of all older persons, at least in the United States and Great Britain, develop some discernible cognitive decline. It is also true that significant cognitive decline of the kind we will refer to as dementia is, in fact, more prevalent among the aged. It exists in one to 1.25 to 1.5 percent of 65-year-olds. But it increases. If you use the so-called Eisdorfer fudge factor, it roughly doubles with every five years of longevity; thus it is about three percent of the 70-year olds, six percent of the 75-year olds, twelve percent at 80, and so on, proceeding to about fifty percent by the age of 90 to 95.

There is good news and bad news. If you live to be a hundred, the odds are 50-50 that you will not be demented. On the other hand, the majority of your friends may. The important thing though is that the vast majority of people do not become demented before they expire, given the current longevity.

The second misconception about senility relates to the issue of treatability. In the past several decades, a classic conflict of medicine has arisen dealing with chronicity versus curability. Medicine is now more and more the treatment of diseases that don't have quick cures, but involve a different kind of relationship between the physician and the patient.

This is true also of diabetes which, of course, is the classic model. The notion that once diagnosed, assuming an accurate diagnosis, the patient should be dropped because there is nothing that can be done to cure, is a very erroneous notion, and one that I plan to examine as it relates to the chronic and progressive dementias.

Senile psychosis was a term used as a matter of convenience to get people into state hospitals. Senile dementia, the most commonly used term today, presumes a difference between the so-called senile and presenile dementias which, in fact, we no longer believe exists.

Chronic brain syndrome is a marvelous example of a misnomer, the assumption being that there is a misuse of the English language. Chronicity is a temporal issue, acute is its converse. In fact, we use the term acute to mean treatable or curable, and we use chronic to mean irreversible or not curable. Indeed there are a variety of ways to get an acute noncurable illness, a crow bar rapidly impacting the middle of the skull, can do a very effective job of generating an acute brain syndrome, probably not curable in most instances. On the other hand, one can have a chronically developing cognitive problem from a worsening depression, which can be very curable. Thus, the terms acute and chronic are probably misnomers. My favorite is OBS, organic brain syndrome, and organic brain disease. Frankly, when I discover someone with an inorganic brain disease, I will grab my tails and white tie and get ready to go to Stockholm for the next Nobel ceremony.

Dementia is the term we are proposing now, and it has an important meaning. It no longer assumes a diagnosis. It is a symptom, a loss of intellectual ability of sufficient magnitude or of severity to interfere with social or occupational functioning. It involves not only intellect but a range of areas of cognitive function. The diagnosis of dementia, based only upon disorientation, is probably erroneous. By the time orientation is impaired, the patient is well along the way of a particular process. There are a number of areas that the psychologist looks for, and I want to call your attention to a few of them because they are important.

Memory is a classic area of impairment, but most of us who are clinically familiar with the disease know that attentional deficits may be more predominant in certain patients than a memory deficit. We don't have a good test for attentional deficit, but those of you who work with the hyperactive child have seen what impact an attentional deficit can have. Those children were formerly seen as mentally retarded, stupid or bad. It was a long while before we recognized that the attentional deficit was the primary difficulty. The only subjective example of such a problem I can give you is what would happen if you took a home movie or a television camera, and moved the camera back and forth very rapidly. Essentially, the input would be moving too rapidly for you to fix it, since you would never get the material fixed in your mind, obviously, you could not reproduce it. We think subjectively that something like that may be happening in the area of attention in some of the dementias of later life. The attention span shortens in some of the older patients. It is not so much memory, but learning about the attentional deficit which may be valuable in attempting to treat such patients.

Learning, it should be remembered, requires not only attention and memory. Learning is a higher order function which also involves reproducibility. A patient has to do something, or think something. That thinking or doing has to have a consequence. Learning involves output. I say this because some of the deficits of these patients are output problems. Some patients may have input problems, some may have associational problems, some may have output problems, and they can easily be misdiagnosed.

Communication problems are often the first symptoms we observe in the patient. We have seen a number of families who have started in group or individual therapy because of a breakdown in communication. The wife thinks the husband is having an affair and beginning to ignore her, or vice versa. Often they begin to lose friends, and social skills such as their bridge playing ability get impaired. The predominant symptom becomes interpersonal communication, and nobody recognizes that.

In fact, the aged patient is inhibiting the communication because he or she cannot remember the train of speech, or names become lost, and so on. This occurs long before orientation problems exist. Orientation does make a difference, obviously, the classic impairment of knowing time, place, and person does show up. The sense of person holds on for a long while. Numerical skills may differentially drop out, as well as reading, writing, and thinking. Thinking skills may be impaired primarily because the material to be processed does not get in, or the answers are forgotten right in the middle of their explanation.

Defects in social skills are reported to be more impaired in the multi-infarction dementia. The documentation of this, however, is elusive. Hallucinations or delusions are rare, but should be watched for. They are serious signs but they should not necessarily mean that the use of major antipsychotic medications is immediately indicated.

The misuse of psychotropic medication, with a group of demented patients, will be discussed later. For the moment, let me alert you to an important issue. The medical community, in general, prescribes much more psychotropic medicine than does the psychiatric community, specifically. I suppose that nonpsychiatric physicians have taken the position, for a couple of centuries, that psychiatric therapy did not do much good, so the psychiatric drugs can't be all that powerful.

However, antipsychotic medications are among the most toxic to the organism and need to be treated with the same precautions as one would use with oncologic medications.

Drugs are used for disorders, not just for occasional symptoms. It should be recognized that most of the antipsychotic drugs impair cognition and make the patient more cognitively depleted. The ratio of benefit to negative effects needs to be mediated accordingly.

Aggressivity is a very common feature of almost all organic conditions, and I don't mean just organic brain syndrome. I mean almost all disorders, especially if aggression is present to begin with.

It is important to understand this for another reason. We have learned about aggressivity, because the family is usually quite surprised by it. It can be very traumatic to suddenly have the husband or the wife become violent, angry, or irritable with no apparent basis.

The primary disorders of cognitive functions are mainly neurologic degeneration of the Alzheimer type, multi-infarct dementia, depression, and the reversible dementia of organic etiology. The last two categories account for about 35% of the people who were not previously seen by a physician. If you do a home-based diagnostic and treatment program, or if patients are brought in by their families to see a physician, one third of the dementia cases will be primarily reversible. About ten percent of the cases will be depressed, about 25% will have a treatable medical disease.

There is still a large segment of the medical community that believes most nonreversible dementia is caused by vascular change. This is probably not true. Of 100 patients with dementia that is not reversible, probably 50%-60% have Alzheimer's type dementia. The neuropathologic changes, at any age, are not distinguishable from that of the so-called presenile dementia of the Alzheimer type. We are calling it a primary neuronic degeneration, in the absence of unknown etiology. The second category of nonreversible disorders is the multi-infarct dementia. This accounts for about fifteen to twenty percent. The notion that arthrosclerosis, per se, causes dementia is probably not accurate, it is more likely a series of micro and mini infarctions. That is important because it tells you something about the characteristic of the disorder. Thirty percent or so of the neuropathologic lesions are mixed primary neuronal and multi-infarct dementia.

The list of other nonreversible dementias is most extensive.

Creutzfeldt-Jacobs Disease is caused by a transmissible slow virus-like particle. The discovery of transmissibility has also led to the notion that Alzheimer's Disease might have a viral etiology.

The reversible base list is a long list, but worth remembering. It is not intended to be a list of everything that can happen to people you don't like. It is, in fact, a list derived from patients who have come in with dementia which reversed.

For example, alcoholism, over the counter preparations, and illicit drugs are important contributors. The data we have on alcohol in older people indicate that alcoholism seems to be bimodal in prevalence. It peaks in the forties, that is, people start being alcoholics in their twenties and they seem to die a little young, but alcoholism is manifest in the forties, and then it seems to drop off. The social drinker who is 50 and 60, in some cases, becomes the alcoholic at 60-70. New data indicate that there is as much alcoholism in later life as there is in younger life . . . about ten percent of the population. There are also three or four studies that reported on the medical and surgical services of general hospitals; the rate of alcoholism or alcoholism withdrawal among men is as high as 20%.

Alcoholics rarely die of alcoholism. They usually die of the same kind of things everybody else dies of; they just die five years younger. In some unknown way, alcohol exacerbates a lot of other metabolic processes and diseases; it certainly complicates other disorders. Obviously, we know about alcoholic psychoses which are predominantly nutritional deficits.

Over the counter preparations are used quite extensively by older persons, illicit drugs are not a serious problem but worth mentioning.

Structurally, my neurosurgical colleagues tell me that one of the main causes for dementia in the emergency room that they see is subdurals.

Normal pressure hydrocephalus, a relatively recently described phenomenon, consists of a triad of a gait disturbance, eneuresis, and dementia. It is important because it is treatable by the use of a neurosurgical shunt. Having said that, the notion that if you have a patient who has a dementing illness, and you cannot find anything else that is wrong, he should be shunted is wrong. About 40% of the patients who go to surgery will have some kind of residual problems, shunts don't always work, and there is a mortality risk. Having now taken care of a number of these patients, I can tell you it is a lot easier to take care of a demented patient without a hole in his head than with one.

There is an enormous toll on the family over and beyond the economics. It is not again a treatment that should come "if there is nothing else that will work, let's try one of these." Unfortunately, I can assure you that this approach is often taken. Families in desperation will go to any lengths to try something which may help.

Infectious disorders, this is information for one additional reason. You all know that the temperature regulation in the aged is different. Hypothermia is, of course, a serious potential disorder. In late life, a failure to spike a fever in the face of an infection may also occur.

Last year, I spent six weeks on the Geriatric services at Ben Gurion Medical School. Demented patients were sent to us from medicine. One woman seemed to have some kind of immune reaction. It turned out, she just had sepsis that was afebrile. This lady was very near death by the time we saw her. The principal signs were dementia. Internists don't like to take care of people with dementia because they think that all people with dementia are crazy. Nobody wants to take care of crazy people in the medical ward.

Remember *socialization.* Nursing homes are perceived by a lot of people as strange places. A particular word of caution to physicians: a lot of the patients you see in long term care have been on psychotropics for some time, and have developed the early symptoms of tardive dyskinesia, which can be very embarrassing to the patient. They will not want to eat in public, so they simply don't eat. Malnutrition can exist even in the face of a very good nutritional program. I say this because recently, while on rounds, a medical student reported that there was no evidence in a female patient of any tardive dyskinesia. After she and I talked, I had to ask the medical student why he thought she kept sticking her tongue out at me. I am sure this lady was very, very concerned about the movement which was uncontrolled and hostile. Be careful, particularly with long term psychiatric patients.

Perhaps the major cause of reversible dementia is medication, and the major basis for that problem lies in prescription drugs. Ten percent of the aged consume 75% of the medication, with a compliance rate of about 50%. There is, in fact, a lot of borrowing, a lot of lending, particularly when there are high densities of older people, and particularly when well meaning friends and family in the health profession, (doctors, nurses, anybody who works in the hospital who has access to drugs) act as feeders. Patients may have multiple doctors, and then are likely to get multiple overlapping prescriptions. Very often, patients won't tell one physician what another physician prescribes or that they have seen another physician. They also don't throw out medications. My recommendation is to have the patient bring with them all the drugs they are now taking. The results may be startling. I think research in the office is really some of the most important kind of research, but it starts with the single patient. The record I know of so far is 40 concurrent medications being taken by a single patient in a given day on an ongoing basis.

As I indicated earlier, the classes of drugs that are most likely to lead to reversible cognitive disturbance do tend to be the antipsychotic or the psychotropic drugs. The last analysis we did of a very distinguished hospital, revealed that of the last 100 psychotropic prescriptions given, 85% were prescribed by a service other than by psychiatry, usually by medicine. We analyzed the drugs given, and learned that the biggest prescription surprisingly was not an antianxiety drug, but an antidepressant medication. In 50% of the cases, there was no indication in the chart about why the patient was on an antidepressant. This occurred in a distinguished medical service, where presumably staff is educated, has time, and knows that somebody else is going to look over their shoulder.

It is important to recognize that all of the psychotropic drugs probably have a cognitive side effect, and that the cognitive side effect is not a positive one per se. It is also important to recognize that we probably ought to stop using words like major and minor tranquilizers. The assumption that all psychotropic drugs are in one category, and that some are more powerful than others, is worse than naive. That is advertising. We have to stop being seduced by it. We should think of these drugs in the categories to which they belong.

Antidepressants, which are used for diagnosed depression, are separated into the lithium type medications for bipolar disorders, the tricyclides, and MAO inhibitors for the unipolar disorders. But they must be used for a diagnosed disease. Once you diagnose depression and prescribe a drug, you are writing a prescription for six months; unless you are willing to make that commitment, you should not be writing a prescription. *Sedative* hypnotics are very tricky. If you can avoid using them, avoid it. Brandy at night, or some other similar medication, with or without whole milk, is probably much preferred.

Anti-anxiety medication should be used in case of anxiety, but never prescribed for more than three months. If the patients do not recover from their anxiety during that period of time, you probably are treating another disorder with anxiety as a symptom.

Always in the case of medication, think of the cost risk analysis. For the patient with dementia, the benefits very often outweigh the risk of side effects by a long shot.

Depression is the primary differential in dementia. Remember, don't expect the patients to tell you they are depressed. Older people's depressions often differ. They focus on somatic symptomatology and pain, and will give you the vegetative signs before they tell you they are depressed. They will give a psychologic statement that you will accept, namely, that I have nothing to live for. They are living alone, on a low income, in a miserable neighborhood, and you say, "my God, if I were that poor woman, I would have nothing to live for either. Since I'm not a social worker, what can I do?"

One of the things you can do, besides calling in somebody in social services is, of course, find out whether you are dealing with a depressed patient. This does not obviate the other problems, but it is certainly something you look at. Look at the pain level and certainly look at sleep changes. Remember, too, that older people don't need as much nocturnal sleep as younger people. The need for sedatives and hypnotics may not be something we are familiar with. Also the notion that we need eight hours of sleep is again an advertisement rather than a physiologic fact.

What we do need is deep sleep. Most of the sedative hypnotics keep you in bed longer, and give you superficial sleep, some at the expense of Stage 4 and deep sleep. I mention this because they do the opposite of what you want to happen physiologically.

Loss of libido is not a necessary function of age. I remind you of that as part of the good news of this lecture, sexual function should be looked at as if you were examining a 35-year-old man or woman. Look for the reason why, including the typical reason of the lack of availability of a partner, also look for reactions to changing functions.

An Alzheimer type dementia is characterized by loss of neurons, with widening of the ventricles, thinning of the cortical layer, the frontal cortex, particularly, and a neurofibullary degeneration. There are two kinds of loss, not only neuronal, but also denditric. Some people think that denditric loss may be significant. Why is that important? Because it has been demonstrated, at experiments at the Roosevelt Cancer Institute in Denver, that they can rearborize a neuron *in vitro*. If we are dealing with a disease that is primarily denditric loss, then some future possibility for a rational therapy may be in store.

Within the affected neurons, there appears to be a peculiar twisting of neurofilaments of the kind described by Terry and Wisnewsky at Einstein and others. These are a form of neurotubulin. Why they twist is not clear, but Wisnewsky has pointed out that in these neurons, there is the existence of an insoluble beta helical protein. The existence of such a protein implies the failure of the working of an enzyme. Wisnewsky is now looking for that enzyme which is associated with the creation of the insoluble protein which leads in turn to this pathology intraneuronally, which leads, perhaps to the destruction of the neuron. This is all hypothetical at the moment but at least it's a lead on the disease's etiology. Neuritic plaques is one sign of the disorder. We know that they are really mostly amyloid because now they suggest something is going on with immunoglobulin.

There are structural changes and neurochemical changes. Acetylcholine and metabolytes are in short supply in the brains of Alzheimer patients postmortem. At the Bronx Veterans Administration Hospital, there is research on acetylcholine precursors and its effect on dementia. Choline and lecithin are the specific precursors used in a rational therapy, very much on the L-dopamine model. While there has been no therapeutic efficacy reported, at least we now have a solid biochemical finding and a basis for clinical therapeutic research.

Work from our laboratories indicates that there are also some specific changes in the immune system. It does appear that there is a higher prevalence of the specific HLA antigen. What is interesting, is that all of the patients with the antigen have primarily an attentional deficit more than the specific memory deficit. Using sophisticated psychologic tests, we are able to suggest a basis to disaggregate Alzheimer's Disease for the first time.

Alzheimer's Disease, or so called senility or senile dementia, is where mental retardation research was a few decades ago. It is a hodge podge that we are starting to separate out. We have noted that early in the disorder, immunoglobulin and IGG, are very high in Alzheimer Disease patients. We have found no reason for this. The hypothesis about a slow infectious disease has been unsupported.

Quite clearly, the immunoglobulins are very high, early associated with a rapid drop in immunoglobulin G, to the point that Alzheimer patients are relatively immunodeficient in five to ten years. It is also true that they die younger. Probably therefore, the immune system is somehow involved.

Another theory is aluminum. Dr. Cropper has reported a lot of aluminum in the brains of Alzheimer's Disease patients. The findings were criticized on technical terms but recent electromicroscopic work in Vermont has re-opened the question. His name is now McDougal and he has redone some of the work in Vermont. It has been reported that in the neurons which are affected (in the neurofibullary) tangles, there is a high level of aluminum in the nucleus—three or four times as high.

There are now rash statements about stopping the use of aluminum pots and pans because aluminum causes dementia. There is zero data on that. As it turns out, aluminum is one of the more ubiquitous minerals around.

It has also been reported that in those same neurons, silicone and manganese are also high. Is there some problem—membrane permeability?

Alzheimer's Disease now affects one in ten, and is an increasingly frequent disease. Its course, however, is not well documented. I suggest perhaps there is more than one type. Perhaps there is an A type, a B type, a C type and an N type. I have never seen two patients change in exactly the same way. Some change very rapidly early on, others in a step like fashion, and some seem to be doing fine for several years, and then change.

One patient I followed for about three years was doing fine. He had a concussion, recovered from the concussion, did fine again, and began a slow deterioration for about a year. Suddenly, in a six-week period, he became so badly impaired that he had to be institutionalized. All this happened within a six-week period, after three and a half years of a very gradual decline.

Another point is that we set up the need for full-time institutional care based upon the patient's prognosis; but in reality, you cannot know from the decline in ability alone. You really must consider the hypothecated level of support. Where there is minimal home and community support, patients will need institutional care early. Where there is maximal community support, the patient may never get into an institution.

The notion that families dump patients in institutions is absolutely erroneous. Typically, families keep their relatives at home at great personal expense. Surveys we did over the July 4th weekend of 100 of our families, found 75 of them at home. They had been caring for their relatives on an average of four and a half years after the diagnosis, which usually does not happen until about six to 18 months after the onset of symptoms. They all expressed the need for community help. Families do work harder and the family role is an important role, will continue to be an important role, and thus will keep the patient at home—provided they get certain kinds of support. They need information about emergency and alternative services. They need, very often, self-help support groups. Ours is called Assist.

There is now a national group which is headquartered in New York called Alzheimer's Disease and Related Disorders (ADRDA) Society. Our assist group is a self-help family support program which has been enormously effective, with minimal professional time. Community supports are crucial. Again, you can almost predict that some kind of sum of the family and community support system will predict what happens to the patient. Health care services and the physical environment are important. Getting somebody to make a home visit, and helping the family in its ability to help care for the patient is crucial.

We have now set up a Family Geriatric Service and every one of our families gets a home visit. We now have an environmental check list which was designed by an architect and an environmental psychologist. Simple renovations can make an enormous difference in the family's ability to care for the patient. In some cases, the home is better than the long-term care facility, at least some long-term care facilities.

Physicians need to do a variety of things to improve care, but it is not only physicians. Diagnosis and evaluation are not a one shot event.

When the patient begins to change rapidly, I think re-evaluation is almost always indicated. The secondary disorder imposed on the chronic disorder may be accelerating the loss. There are a variety of treatments. Medication, both the use and withholding of medication, can be very important. The family may need information, advice and referrals for legal and financial matters.

This situation can be really catastrophic for the family. When the person with the dementia is still able to participate, a lot can be done which saves the family finances rather than later on when you have to spend so much, that the family finances can be ruined to get any kind of help.

There are varieties of living trusts, and other financial or legal practices that can be established. We now work with a legal and fiscal officer in one of our banks. They emphasize over and over again, to get patients and their families to them earlier, before it has to go to Court.

Supportive care givers are probably the people who are under the highest stress in the United States. The job of an Air Traffic Controller is nothing compared to the job of taking care of a demented husband or wife for what one of them characterizes as "a thirty-six hour day." They need medical help, probably as much as anybody I know. They also need respite care, and a number of types of prophylactic care that we as a community, should be up to.

For a number of years in Britain, the idea of bringing someone in to relieve the family for weekends so the family can bare up during the remaining weeks is seen as more economical than institutionalizing the patient for 52 weeks, not to mention the attendant family guilt.

The use of appropriate therapy is vital. Families need to know that somebody knows about the disorder. They must be made aware of any changes in development, because the patients are prone to have a variety of problems.

In conclusion, when there is a reversible dementia, pay enough attention to it to reverse it. There is no such thing as senility. There is always a cause for significant cognitive disorder. There is *always* a cause. You may not know what it is, but it doesn't happen as a normal function of age. If the individual has a dementia, and an associated secondary diagnosis, you can take care of the secondary problem, whether it is psychiatric or medical, and reverse that component of the dementing illness. Additionally, we can optimize the patient's environment, both socially and professionally, to provide alternative care to the one that they are getting.

Our patients still drive their cars, go shopping, and work around the house. When we maximize the functioning of the patient, they want it and the family wants it.

Not to be forgotten is the last step of continued education. Most of what is now happening in the field of senile dementia was not even dreamed of as recently as five or six years ago. When a diagnosis was made, the physician said there is nothing I can do, don't bother coming back. We have documented superb neurologists and psychiatrists saying there is nothing I can do.

It is just not true. There is an enormous amount you can do. We are talking about probably two to two and a half million patients, and if you magnify that by the number of families involved, you can see that there is a need, and there is an opportunity.

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Prospects and Advances in Geriatrics

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Many institutional and scientific advances are taking place in, or are in prospect for, gerontology and geriatrics today. History may show that, despite many contemporary difficulties, we are living in a watershed era.

Improvement in the organization and delivery of services to a growing elderly population depends on meeting goals of quality and economy at the same time. Achieving these goals depends, in turn, on knowing what we are doing, that is, a productive scientific base for effective diagnosis, treatment, and prevention. The relationship of costs of care to research is elemental: there is nothing so wasteful as ineffective attempts at treatment.

In this sense, research and service are inescapably connected with one another, and both relate to costs. Through the evaluation and application of existing knowledge and the discovery and application of new facts, we lay the surest basis for controlling costs and achieving our humanitarian aims.

Essential to organizational or institutional improvement is the development of a leadership cadre in geriatrics. Well-trained professionals are absolutely necessary for the growing number of endowed or soon-to-be endowed chairs in geriatrics. The specialized personnel needs of clinical programs, research enterprises, long-term care institutions, retirement communities, and university teaching programs cannot be ignored if we are to meet the needs of older Americans, now 25 million.

Unfortunately, few people at this moment have adequate training, strong commitment, and supportive intellectual resources necessary to establishing leadership roles in geriatrics within medical schools and other professional settings.

The National Institutes of Health has assisted in the development of new fields of research, and new types of laboratory and clinical investigators. Teacher-investigator awards are one means of doing this. The National Institute on Aging has established a program for physicians who, after their residencies, wish to prepare for research and teaching careers that emphasize geriatric medicine and related clinical disciplines. Each five-year award helps create a permanent place for geriatrics and gerontology in the medical school curriculum.

The NIA Clinical Investigator Award, established in 1978, educates superior candidates for independent biomedical research careers in areas relevant to aging and geriatric medicine. Three-year support is provided for persons with health professional degrees and four to seven years of postdoctoral clinical and research experience. The award is designed to provide intensive, guided research experience for clinicians in organic diseases of old age, clinical immunology, endocrinology, epidemiology, and other disciplines related to diseases among the elderly.

Also part of our strategic armamentarium is the NIA Geriatric Medicine Academic Award. Developed by the Institute to improve the quality of the curriculum in geriatrics, this award to medical schools fosters research in geriatrics and encourages students to seek careers in this field. A counterpart is the NIA Geriatrics Dentistry Academic Award.

A major obstacle to the development of gerontology and geriatrics is the large decline—30 or 40 percent—in young physicians entering research careers. Moving into a research career means foregoing a handsome income from practice, a sacrifice of considerable significance if the young physician has a family to support.

Another obstacle is the dearth of research money. The large developmental funds made available to NIH institutes after World War II are nowhere to be seen. The National Institute on Aging, originating in the 1974 Research on Aging Act, had its infancy at a time of large governmental cutbacks. These, of course, affected other institutes. Thus, there is little direct stipend support

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in medical schools for attracting students to research in aging. The NIA is eager for private-sector involvement, and negotiations are under way with foundations and corporations to join the public sector in providing support for the advancement of training and research in geriatrics and gerontology.

The progress of geriatrics and gerontology has been limited by the absence—within conventional medical education—of settings and arrangements to promote training and research on age-related diseases, long-term care, normal aging, and the maintenance of health of the elderly. This can be remedied by establishing a counterpart of teaching hospitals to deal with research and training issues in long-term care, that is, teaching nursing homes affiliated with academic health centers.

This country has about 7,500 community hospitals and about 450 teaching hospitals. There are 18,000 nursing homes, but none have the contemplated teaching and research functions and affiliations with medical and other professional schools. One result is that 1.3 million people in these nursing homes are outside the mainstream of academic medicine and nursing. Incontinence, immobility and senile dementia—the main medical reasons for their institutionalization—are rarely the subjects of research to improve diagnosis and treatment. Without this, we may limit ourselves to repeating ineffective and inefficient procedures, the costs of which are enormous and growing.

In 1976, the nation paid $9.9 billion for nursing home care through private and public channels. In 1980, the bill exceeded $21 billion, more than doubling in just four years. By 1990, nursing home costs are projected at $75 billion.

I want you to note two assumptions on which the projection is based: 1) the yearly net increase in the elderly population, those aged 65 and older, will be a half million; and 2) major liberalization of Medicare and Medicaid benefits to expand home care is unlikely. The assumptions are silent on development of knowledge and technology either to prevent the disturbances, disorders, and disabilities that produce nursing-home admissions or to allow patients with these problems to remain at home.

All of these considerations feed into the concept of the teaching nursing home and add to the urgency of its materialization. Funding possibilities are being investigated. Discussions are under way with the Health Care Financing Administration (HCFA), which sets Medicare and Medicaid reimbursement rules. These might provide some necessary funds for supporting patient care activities in teaching nursing homes. Research projects there could be supported by conventional grant mechanisms of the National Heart, Lung, and Blood Institute, National Institute of Neurological and Communicative Disorders and Stroke, and other institutes, besides the NIA.

In addition, the NIA is exploring the possible use of center grants to support administrative and research functions envisioned for the teaching nursing home. With long-term support, the institution could establish the necessary collaborative arrangements with teaching hospitals and professional schools in the university. It could also identify and organize sources of patients for participation in geriatric research, not only within the walls of the teaching nursing home but elsewhere as well. The teaching nursing home would be a meeting ground for a variety of health and social service professionals, thus introducing young practitioners and scientists to team methods of providing care and conducting research.

In initiating its part of the concept, the portion closely related to biomedical research, the NIA will insist on strong affiliations of high quality nursing homes and academic centers with a strong commitment to geriatrics. The NIA program will necessarily be small, but there will be no compromise on the requirement of bringing regular faculty along with students into a model research/training environment. I refer not only to medical faculty and students but also—sooner or later—to their peers in nursing, speech pathology, occupational therapy, dentistry, other health fields, and social service professions. All must have an opportunity during training to work with and understand the elderly. For this growing population, especially the rapidly growing segment over age 80, will account for an even greater portion of practice time in the future than they do today.

Let's turn now from organizational to scientific prospects and advances. Scientific advances in gerontology and geriatrics can be discussed in terms of studies of human aging and research geriatric medicine. A premise of gerontology is that phenomena or processes of normal aging can be distinguished from the effects of disease, disability, and social adversity. The most systematic approach to human aging is through longitudinal studies, in which individuals are compared in many ways to their younger selves. The NIA Baltimore Longitudinal Study of Aging, for example, seeks to identify types of change and the rates at which they occur over long periods of the human lifespan. These and other studies have contributed to considerable scientific sophistication about human aging in recent years.

By comparison, research geriatric medicine has lagged behind. Its function is to examine age-related diseases and disabilities and the influences on them of psychosocial and other factors. Much ground-breaking remains to be done.

Obviously, studies of human aging and research geriatric medicine overlap to a large extent, findings in one area illuminating issues in the other. With this in mind, I will note a few recent advances. At the NIA Gerontology Research Center in Baltimore, Reubin Andres and associates have examined metabolic changes with age, specifically glucose metabolism and various tests of glucose tolerance. A decade ago, these scientists questioned conventional criteria for the diagnosis of diabetes based on the performance of young adults on glucose tolerance tests. Under these criteria, most older people would be classified as diabetic or prediabetic. Response to glucose changes normally with age, they found. Under more recent criteria, these physiologic changes no longer are considered to be pathologic and requiring drug or diet regimens. It is fair to say that this gerontologic research helped to set the stage for new perspectives on diabetes.

Also at the NIA Center, examination of 76 *healthy* subjects aged 26 to 89 by S. Mitchell Harman and associates showed no decline in free and bound testosterone with age. This finding controverted many studies in the medical literature; indeed, it became clear that past studies had erroneously identified declining hormone levels as age effects when the patients had alcoholism or other chronic disease.

Other studies that help disentangle disease and aging phenomena might also be cited briefly. Dr. Edward Lakatta of NIA has utilized a novel method of investigating calcium kinetics in heart tissue: using a laser beam, he documents calcium dependent light fluctuations important to the cardiac cycle. Dr. Lakatta and associates, after thorough studies on 40 patients, concluded that digoxin therapy was unnecessary and even risky in chronic heart failure in patients with stable rhythm. Finally, Dr. George Roth of NIA has established that hormone receptors decline with age.

Another kind of fruitful investigation concerns dihydroepiandrosterone. DHEA is perhaps the most abundant steroid in the human body. But we do not understand its function. Noting data that show a decline coincident with mammary cancer, Arthur Schwartz of Temple University treated laboratory rodents prone to such cancer with DHEA. They failed to have the cancer. DHEA appears to have other effects in rodents: antiobesity, antimitotic, and anticholesterol. DHEA-treated animals show less gray fur than untreated rats of the same age. These invesigations may mark the beginning of a new understanding of steroids as they relate to aging. We can only hope that productive leads are confirmed and extended.

Today, we know something about the mechanisms of senescence in various systems of the body. With more knowledge about long-term changes in the immune, central nervous, and hormonal systems, we can begin to control their rates of deterioration.

Science is moving into two explorations: 1) looking at the possibility of maintaining the status quo of a system, and 2) seeking techniques to restore function. Marc Weksler and Gregory Siskind at Cornell have worked on enhancing the immune complex. Carl Cotman at the University of California (Irvine) has evidence of recircuitry or neuroplasticity in the central nervous system: healthy brain cells compensate for adjacent cells that were damaged experimentally. Paul Baltes, in research on fluid intelligence (which is highly cued to physiologic change), has discovered experimentally that intellectual dysfunction can be overcome.

Methods of pinpointing medical problems of the elderly are needed, so we may do a more effective job of treatment and prevention. Recent clinical, laboratory and epidemiologic research has helped to clear away myths that have impeded our understanding of problems of the elderly. For example, senile dementia is recognized as a family of illnesses, some of which are reversible but all of which are amenable to treatment. We are beginning to understand possible organic bases for senile dementia of the Alzheimer's type. We may be lucky and find biochemcial markers in spinal fluid or blood that reflect reduction of brain neurotransmitters associated with senile dementia of the Alzheimer's type. If so, research on this dreaded affliction probably will move ahead with greater speed.

I expect increasing efforts to find biomarkers for normal aging in hopes that they may aid in assessing nutritional, hormonal, immune, drug, and other interventions as they may bear on retarding normal processes of aging. In a pioneering effort at the NIA center in Baltimore, Gary Arthur Borkan and the late Arthur H. Norris introduced a pattern profile quite different from the conventional chase after some elusive, single marker of physiologic age. Their profile-oriented approach, mining the rich data of the Baltimore Longitudinal Study of Aging, may be the beginning of a fresh approach to assessment methodology.

With so much to do in the context of resource limitations, the capacity to identify significant findings and fertile lines of research becomes extremely important. NIA is attempting to sharpen its own abilities to follow the work of its 400 grantees and evaluate the content not only for scientific validity but also for additional investment in the context of national needs. It is time for the NIA to employ a tougher and more sophisticated examination of what studies of aging and research geriatric medicine are producing.

The Congress has been relatively generous to the Institute, up to now one of the fastest growing institutes in the history of NIH. The caliber of research proposals has grown; aging research applications as a group tend to receive priority scores in the same range as those received by other institutes.

This brief review may show you that gerontologic and geriatric research is producing results, have an organizational and funding focus, and have a role pertinent to issues posed by a society concerned about its resources and conscious of the needs of a growing elderly population.

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The Dependent Elderly and Women's Changing Roles

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It is ironic that two of the most influential achievements of this century—the defeat of major infectious diseases and spectacular advances in medical technology—have created a need for vast health and social programs requiring major shifts in the perspective and practice of health professionals. As more people are able to live the full life span previously enjoyed by relatively few, new approaches and new skills are required to deal with the consequences to the health of those whose lives have been prolonged.

It is now a practical necessity for medicine to attend not only to the specific illnesses of older people, but to the health/social supports they require, and to the social environmental context in which they occur. After 35 years of research in gerontology, it is now as fundamental that in the aged, physical and mental health, and social, environmental, and economic factors are interlocked. It is therefore no accident that The Gerontological Society of America is multidisciplinary and multiprofessional. The intertwining of the various influences and the problems of sorting out the contributors to the "state of well being" called health makes gerontologic research and practice complex and difficult, yet fascinating, challenging, and rewarding.

There is concensus among gerontologists that function rather than disease is the indicator of the health social supports needed. Significantly, the Institute of Medicine's report on care of the elderly was not called medical care of the elderly, or even health care of the elderly; rather, it was titled "The Elderly and Functional Dependency" (Institute of Medicine, 1977). The report was consonant with the definition of long term care as "... those services designed to provide diagnostic, preventive, therapeutic, rehabilitative, supportive and maintenance services for individuals ... who have chronic physical and/or mental impairments in a variety of institutional and noninstitutional health care setting, including the home, with the goal of promoting the optimum level of physical, social and psychological functioning" (HRA, 1977). A key word in this definition, of course, is functioning. That is, services include, but are not limited to, medical management.

The net result is that health professionals are involved in a major revolution. We are faced with the extraordinarily difficult task of augmenting and balancing existing methods of individual practice and health care delivery with a new and very different approach called long term care. Responsible professional practice depends on keeping abreast of the changing or emerging needs of different population groups, and on our willingness and capacity to respond to change.

Long term care is necessary because we have made great progress towards squaring the survival curve, but we have not made substantial progress towards squaring the disability curve. In a recent article in *The New England Journal of Medicine,* Dr. James Fries (1980) called attention to the squaring of the survival curve in this century—that is, more people survive the barriers of infectious disease of early life. Dr. Fries expressed optimism about achieving the new goal of squaring the disability curve, which would enable people to live the full life span without disability. To quote Dr. Fries' predictions, "The number of very old people will not increase .... chronic disease will occupy a smaller proportion of the typical life span, and the need for medical care in later life will decrease."

Such encouraging but overly optimistic statements can be used as a rationale for regressive social policies. If older people are not going to be sick, frail, or disabled, why develop a costly supportive service system? The reality is that the very old population is increasing most rapidly, that is, those who are most disabled and dependent upon others. From that population come most of the million and more older people who are so disabled that they require round-the-clock care in nursing homes, two million equally disabled who are not in institutions, and six million more who require less intense services.

A longitudinal rather than a cross-sectional perspective tells us, that of the two-thirds of all older people who are not in need of services but are currently moving toward advanced old age, more and more who survive will become functionally disabled. More will be institutionalized. More will suffer the interpersonal losses and social disabilities inimical to health. We have not achieved the scientific breakthroughs that will prevent or cure the chronic ailments that cause disability and dependence on others, for example, Alzheimer's Disease. Squaring the disability curve also entails dealing with the basic conditions of life that can produce and exacerbate disability—poverty, inadequate housing, dangerous environments, and the absence of needed health social services.

An emphasis on long term care is sometimes misconstrued. Sometimes its position vis-a-vis the acute care system is couched incorrectly in either/or terms. The most common expression of that inappropriate dichotomy is the medical model versus the social model. Both approaches are necessary. The goal is to link one to the other. No matter how sophisticated a long term care system might be, older people need a high order of meticulous medical care for both their acute problems and for exacerbations of their chronic conditions. They are admitted to hospitals three times as often as younger people and stay twice as long. Furthermore, the hospital is often the point of entry into the long term care system, and those needing long term care frequently need acute care. Long term care, therefore, cannot be a substitute for acute care. The two are interdependent and must complement each other. Inadequacies in either system increase the burden on the other.

The principal provider of long term care services to the noninstitutionalized elderly is the family. We professionals refer to ourselves as the providers. Yet, it is still the family members who provide 80% of personal and medically related care, such as injections, bandage changing, and medications to the older people in need of home care. It is family members who provide 90% of all inhome and other services, such as personal care, household maintenance, meal preparation, continuous supervision, transportation, mobilization coordination, and monitoring of services from other sources. The 90% estimate was arrived at by the General Accounting Office, as an outcome of its Cleveland study. Not included in the calculations of the services families provide is the concentrated and demanding intermittent care needed at times of acute illness, such as interest, concern, and overall dependability and emotional support.

The family, then, is a full partner in the long term care health enterprise. The physician's prescription for treatment depends on its practical implementation on the family. Families cannot be viewed only as providers or resources for care, although they are that. Unless our perspectives and services include the needs of the family members themselves, we may contribute to the creation of new population groups at high risk of mental and physical stress and breakdowns. Such perspective requires the understanding of older people's family relationships. Yet, that subject is one of the most misunderstood aspects of the aging phase of life or, for that matter, of any phase of life.

Accurate and realistic information about the aged and their families is basic to the resolution of a social policy issue. The issue is the appropriate mix of services and support for older people that should come from what is being called the natural or informal support system of family and friends, and those that should be provided by the formal system of government and agencies.

Depending on the nature of the evidence, we can take different paths. If, for example, the family has the capacity and willingness to care for older people who need long term support, little would be needed in the way of a formal system. If the family has the capacity, but not the willingness, then our efforts should be directed to acknowledging the family's efforts, rather than burdening the taxpayer with the cost of health social services. But, if the family is willing, but does not have the capacity to provide all the services needed by its elderly members at all times, then a responsible society and responsible health professional must develop the programs needed to buttress and supplement the family's efforts.

Unfortunately, misconceptions and biases impede practice and planning by stubbornly ignoring the evidence. The basic myth is that families are alienated from the aged. This pervasive and persistent myth assumes that older people are isolated from their families, and that family behavior toward the aged has changed since the good old days. The good old days are viewed romantically as a time when multigenerational families lived together harmoniously in contrast to today, when intergenerational contacts are infrequent, and when the elderly long wistfully to be taken into their children's homes, but are rejected.

The facts are different. Older people prefer to live near but not in the same household with their children. Mainly, combined households result because of economic considerations or because the health of the older person requires it. The vast majority of older people with children live close to at least one of them, and see them frequently (Shanas, 1979).

At no time in history was the three-generation family ever the common mode if only because there was little overlap of three generations. There is even less evidence that, when such households did exist, they were harmonious. Though strain and conflict in such situations are not necessarily present of three generation households in one study, the families themselves described the arrangement as hazardous, requiring the virtues of a diplomat, a statesman, and a saint. In short, there has been thorough documentation of the strength of intergenerational ties, and the continuing stronger expressions of responsible filial behavior. Not a shread of empirical evidence to the contrary has been produced. Despite the evidence, however, not only has the myth survived, but it has created several other myths.

One of those myths is the myth of service substitution. It assumes that the provision of services by the formal system replaces family services, encourages the family to shirk its caregiving activities. Of course, community services are so grossly underdeveloped that we would be hard put to demonstrate such a proposition. The available evidence is that formal support complements and supplements family support rather than substitutes for it. An important study carried out in New York under the direction of Janet Sainor, Commissioner of Aging, when she was the head of the Community Services Society, found "that professional coordination of formal and informal support enhances the quality of family care by relieving the pressures of the family system" (Horowitz, 1978).

A particularly malignant myth is that families repay the devotion of their elderly parents by dumping them into institutions. Many studies of the paths of older people to institutions have shown that institutionalization is the last resort for families, when all alternatives known to them have been explored, and the family has exhausted itself in the process, economically, emotionally, and physically. When the family makes the placement, they do so reluctantly, and suffer severe emotional stress and guilt in the process. Or, the family members themselves are too old, too sick, or too burdened to provide the needed care.

The role of family is illustrated by the characteristics of institutionalized older people. With an average age of 82, they are almost a decade older than the total elderly population. They are much more impaired physically and functionally. They have multiple diagnoses, and most need help in walking, dressing, feeding, and bathing. The institutionalized elderly are much more impaired mentally, with about three quarters of them having some form of mental impairment; between 50%–60% have some degree of chronic organic brain syndrome and another 17% have functional mental disorders. The vast majority of them are depressed.

Parenthetically, though there is such a high concentration of mentally impaired older people in institutions, a recent report of the American Psychiatric Association found that practically none of the institutionalized had had any contact whatsoever with the mental health system before admission (Glasscote, 1976).

As significant as the impairments of older people in institutions, is their family status. Those in institutions have many fewer family resources. About ten percent of them are married, compared with about eighty percent of all older men, and about fifty percent of all older women. Only about half of the institutionalized have a surviving child, compared with about 82% of all older people who are not institutionalized. A careful analysis of national data found that each additional child a person has, reduces the chances of being institutionalized in old age (Soldo and Myers, 1976).

Severely disabled people who are not in institutions live with their families, and they outnumber the institutionalized, two to one (Brody et al, 1978).

There is still another myth, which could be called the mea culpa myth. We in the United States blame ourselves for being alienated from our own old people. We point to other countries wistfully, particularly the developing nations, as maintaining higher standards of respect and care for their aged. The sheer demography mitigates against such comparisons. It is one thing to talk of a very large, very old population in need of family support (one in every nine Americans) and quite another to talk of a smaller proportion of older people who are younger. For example, about two to three percent of the total population in Africa and South Asia, or three to four percent of the total population in Latin America and East Asia are classified as elderly. In 1975, people aged 60 and over, were 7.3 percent of the population in China, 11% in Japan, but 15% in the United States. In India, people 50 and over are only 9% of the population.

The overwhelming evidence is that families have been steadfast as the principal provider of services of all kinds to older people. This should come as no surprise to health and social professionals, because we are well aware of the role of the family in the development of personality. We are aware of the continuity over time of both the individual personality and the family personality over time. We know that the well functioning family whose caring relationships have deep historical roots does not suddenly abandon a sick older person. Nor does the malfunctioning family, characterized for a half century or more by distance, alienation and conflict, suddenly mobilize itself to give loving care to impaired older people. Certainly, a minority of older people is abandoned by families, but so is a minority of small children beaten, abused and even murdered. There is no one stage of the family life cycle that has a monopoly on psychopathology.

Does the continuing responsible behavior of families mean that we can safely leave the health care of older people to those families? Fifteen years ago, it was pointed out that dependencies of older people had already gone beyond the self solution, and the kinship-solution, to require societal solutions (Blenkner, 1965). Societal solutions were grossly inadequate then and they still are now.

Meanwhile, two major social phenomena, both relevant to the family's role, have gathered momentum to widen the gap between need and action. The first trend is the demographic imperative previously mentioned. Demands for parent care have increased vastly with the rapid persistent increase in the size of the elderly population. People 65 and over have increased from three million or about four percent of the population in 1900, to about 25 million or 11% of the population at present (Brotman, 1960).

Even more significant than the numerical proportionate increase, has been the changing age structure of the aging population itself. The 75 plus group has grown much more rapidly than the 65 to 74 group. People 85 and over have grown most rapidly of all. This is projected to continue between now and the year 2000; people 65 to 75 will increase by about 25%, and the 75 to 84 group will increase by 57%; but the 85 plus group will almost double. The very old are the ones most vulnerable to the physical and mental assaults and disabilities that require the help of other people.

The demographic changes have also radically altered the family demography, specifically the proportion of those in need of care relative to the available care given. Rates of widowhood rise with advancing age and, of course, of those widowed most are women. At 75 and over, 70% of all women are widowed. There are nine million widowed people over age 65 in the United States. During the same time span in which the elderly population grew, people tended to have fewer children, further reducing the family resources available in old age. A particularly poignant result of being very old can be the loss of an adult child by death. This is happening, unhappily, more and more frequently.

Any additional biomedical progress that prolongs life even further, or makes additional progress toward squaring the survival curves, would further increase the number of dependent aged proportionate to the pool of potential care-giving children. It has been calculated that the proportion of people in their early sixties who have older parents and relatives alive is increasing at a dazzling pace (Sheppard, 1978). In 1960, there were 34 older people who were 80 years of age and over for every 100 people in the 60 to 64 year-age group. Within ten years, that ratio will change to 63 per 100 and, by the year 2000, there will be 79 per 100.

The family is usually viewed downward from the prospective of the old. Thus, Shanas' (1980) recent data inform us that four out of five older people have at least one adult child, and ninety percent of those with children are grandparents, and 46% are great grandparents. Forty-six percent are at the top of a four-generation family. If we look upwards at the family tree, from the perspective of the young, the changes in the family structure are dramatized. It becomes apparent that at every age, people have more grandparents, and more great grandparents. As the older population grows older, so do their children. About one-fourth of the people in their late fifties have a surviving parent, and about ten percent of people who are 65 or over have a surviving parent. When the need to provide care arises, then, adult children most often are in middle age, and may even be in early old age. They may be facing retirement or may already be retired. They may be experiencing the onset of age related chronic ailments, lower energy levels, and interpersonal losses. Yet, families continue to go about their business of caring for their elderly family members.

Research has been concerned with establishing the precise identity of the principal family care givers. Currently, alternatives to institutionalization are being advocated. The natural or informal support system has been discovered, and the family is being cheered on in its care giving roles. It has become clear, however, that these words and phrases are only euphemisms for the adult daughters and daughters-in-law, who are the true alternatives.

If the impaired older person is married, the vast majority of services are provided by the spouse, together with the daughters, or the daughters-in-law. When the older person is widowed, the women in the next generation are the principal care givers. Generally, older people in need of help look to their daughters rather than to their sons for assistance, and the daughters respond. They not only provide all the household and personal care and other services previously mentioned but, when it is necessary for an older person to move in with the child, more often than not, it is the daughter who provides the home. This does not imply a lack of responsibility or a lack of family feeling on the part of the son. Rather, it reflects the cultural assignment of gender appropriate roles.

The capacity of women who are the principal and traditional providers of parent care to continue in that role to the same extent as in the past is now questioned. The lives of women have been undergoing a radical transformation as they have entered the work force at a rapid rate. The proportion of women of all ages who work has quadrupled in the past half century. At present, more than half of all women of working age are actually in the labor force and, incidentally, this situation is not unique.

Publicity about women working usually focuses on young women—the increasing numbers who achieve advanced educational levels, their entry into jobs and professions formerly the domain of men, and their rise up the corporate ladder. But the fastest rate of entry into the work force has been that of women between the ages of 45 and 64. At present, 56% of married women between the ages of 45 and 54 are in the work force, a fivefold increase from 11% in 1950. While young and single women used to predominate the work force, now most working women are middle aged and married. Sixty percent of women between 45 and 54, and 42% of women between 55 and 64 now work.

Undoubtedly, the women's movement and changes in attitude about gender appropriate roles have been influential in producing such statistics, but other forces have been operating as well. The rise in divorce rates send many women to work. Many women have fewer children to keep them at home than did previous generations, and the creation of accessibility of labor saving devices for the home results in more free time. Increasing educational levels have stimulated career interests. Additionally, the rising cost of living compels many women to seek paid work and many couples enjoy the high standard of living accessible to the double income family. Though career commitment and self fulfillment have accounted for many women working, the pull of employment for most is that they and their families need the money.

To recapitulate briefly, the fruits of past research have documented continuing responsible familial behavior from the old, strong family bonds across generations, and the major role of the family in avoiding institutionalization. But the sweeping demographic and life style changes have potential for disrupting these patterns.

Recent studies, many of them still under way, are examining the effects on the care givers and on the total family. Although far from complete, the mosaic is taking shape as information is added bit by bit. Some information was reported for the first time last week in San Diego at the annual scientific meeting of The Gerontological Society of America. One series of studies is being carried out by our research group at the Philadelphia Geriatrics Center. "Women in the Middle" and Care of the Dependent Elderly (Administration on Aging, Grant #90-A-2174). The Dependent Elderly and Women's Changing Roles (Administration on Aging, Grant #90-A-1277).] As a first step, we interviewed three generations of women, grandmothers who were 65 or over, their middle aged adult daughters, and those adult daughters' young adult daughters. The young women had an average age of 22.

One question we explored was whether attitudes about family care of the aged are changing across the generations. We found that the vast majority in all three generations resoundingly endorsed the traditional value of filial responsibility to the aged. That value has remained sturdy, despite the emergence of the new value of women working. Both the daughters and granddaughters expressed their willingness to be depended upon by the old. Interestingly, the granddaughters felt more strongly than their mothers, and very much more strongly than their grandmothers about what we are calling grand-filial responsibility; that is, that older people should expect help from their grandchildren, and that the grandchildren should give it. Of course, the attitudes of these young women may reflect their age, their life style, and their inexperience rather than a generational trend. At the very least, however, they indicate a vigorous survival of family feelings of responsibility.

Paradoxically, despite the fact that all of these women repeatedly endorsed filial care, three quarters of them also subscribed to the myth of alienation. They agreed that these days, adult children do not take as much care of their elderly parents as in the past. Like most people, they apparently feel "my family is behaving responsibly, but all those other people out there are not."

We also asked the women about their attitudes towards gender-appropriate roles. Most members of all three generations expressed views that are generally attributed to the women's movement. For example, they felt that child care, household tasks, and parent care should be shared equally by men and women and that daughters should be encouraged to the same extent as sons to go to college. Within the context of this overall agreement, however, there were significant trends across the groups. Each successive generation gave stronger endorsement to such views, with the granddaughters being much more emphatic than their mothers and their grandmothers.

The husbands of the middle generation women were asked some of the same attitudinal questions that we had asked their wives, about filial responsibility and gender appropriate roles. As might be expected, when partners in enduring marriages are concerned, the husbands agreed with their wives. They endorsed family care of the aged, and they said men should share child care, household responsibilities, and even parent care.

However, it must be remembered that those data report attitudes, not behavior. Attitudes and behavior are not identical. We cannot assume that the men's or even the women's opinions that husbands and brothers should share responsibilities are now or will in the future be translated into action.

Women themselves with deeply internalized social strictures and ingrained behavior do not always expect men to share. Studies of young couples indicate that real change in the patterns of sharing household and child care responsibilities, is neither widespread nor profound.

If young people have not made significant changes in the sharing of their household and care giving activities, is it reasonable to expect that middle aged couples will move quickly to share parent care?

In specifying their view as to how filial responsibilities should be expressed, all three generations of women in our study distinguished family responsibility from the provision of concrete services. The vast majority of all three generations, for example, preferred adult children for intimate functions such as confidant and financial management, but they favored paid workers for concrete services rather than obligating a working daughter to give up her job. The middle generation women were much less willing than their elderly mothers, to depend on their children in old age for financial support, or for personal care, meal preparation, or housework.

Parenthetically, although there were strong trends across generations on many variables, ethnicity accounted for even more variance than generation membership, particularly with respect to preferences for service provided. Ethnicity has been characterized as the lurking variable by Johnson (1980) because it accounts for differences that underlie the usual analyses of data in terms of groupings such as race, sex, and family composition. She states that the usual racial breakdown by black or white is simplistic and inadequate because there are intrablack and intrawhite differences that have important implications for the design, acceptability, and effectiveness of health care delivery.

If we look at our Philadelphia Geriatric Center data for clues as to the future allocation of service provision between the formal and the informal support system, it becomes apparent that the giving of money and the provision of concrete services (such as household maintenance and personal care) are not equated with the family feeling. There are different meanings to depending upon different people for different things. The formal support system was not only more acceptable to the middle-aged women in the study (the next cohorts of older women) but was actually preferred as the provider of money and concrete services.

The situations of these middle years women make us wonder to what extent they were saying they didn't want their own daughters to experience the strain that they are now experiencing. The older the middle generation women were, the more likely they were to be providing substantial amounts of help to that mother. Of those who were providing some care or services to their elderly mothers, the average number of hours of help given per week rose from three hours, when the daughters were in their forties, to 14.2 hours, when they were in their fifties, to 22.7 hours of help per week when they were in their sixties.

As these middle generation women grew older, the type of care as well as the amount changed. Personal care to their increasingly older and more impaired mothers became necessary. The older the mid years women became, the more likely they were to have the impaired elderly mother in their own households.

The older the middle years women were, the more likely they were to be widowed, to have lower incomes, and the less likely they were to have their own children at home. However, working and nonworking middle aged women provided similar amounts and types of care to their elderly parents.

The data from our study are supported by Soldo's analysis of a National Data Set. She found that as women aged from 40 to 60, the number who have living children at home declines. But the number having older people in their households, rises steadily. As in our study, the proportions were similar for working and nonworking women.

It is apparent that theoretical formulations of the family life stages ending in the peaceful responsibility free Empty Nest stage requires rethinking. For many of the middle aged, the traditional Empty Nests are being refilled with impaired older people physically or figuratively in terms of increased responsibilities for parent care. At a time when cost benefit approaches are emphasizing the dollar cost of services, the hidden costs are becoming visible. Those hidden costs may be converted to dollar costs, if the stress on the middle aged and aging caregivers triggers their own physical and mental breakdowns.

Years ago, the classic Grad and Sainsbury (1966) studies in England and more recently, Gurland's study of older people in New York and London (1978), found that the care of ill, older people negatively affects the mental-physical health of the family caregivers. Such care can restrict the family's social leisure activities, disrupt household and work routines, cause family conflicts, and reduce income. Even young children can be adversely affected.

As responsibilities peak in middle years, how do caregivers manage? Cantor's data from her ongoing study in New York indicate that caregivers who work do not relinquish their responsibilities to the old, to other family members, or to their jobs. What they did was to sacrifice their own free time, opportunities to relax, hobbies, socialization, and recreation (Cantor, 1980). Small wonder that two thirds of Cantor's sample of caregivers reported a great deal of emotional strain and almost half reported a great deal of physical strain.

Our own research group has characterized working, parent caring, middle aged women as "women in the middle." As the phrase implies, they are women in the middle not only because they are at middle age, and in the middle from a generational standpoint, but they are in the middle in that the demands of their various roles compete for this time and energies. To an extent unprecedented in history, their roles as paid workers and as caregiving daughters and daughters-in-law to dependent older people have been added to the traditional roles as wives, homemakers, mothers, and grandmothers. We conjecture that many of them are also in the middle because they experience pressure from two potentially competing values; the traditional value that care of the elderly is the family responsibility and the new value of women doing out of home work.

The focus on women in the middle is not intended to obscure the fact that some nonworking women, some sons, some grandchildren, some siblings (even some nieces and nephews of the elderly) are also in the middle. And older people without any relatives in the middle are uniquely deprived.

The woman in the middle is, of course, a prototype. There are wide variations in the ages and the stages of life at which one may become a woman in the middle. Such women have had many different combinations of personal circumstances and come from many socioeconomic, educational, and ethnic backgrounds. Some have worked all of their adult lives; others entered or re-entered the labor force in their middle years or plan to do so. They have varying personalities, and adaptive capacities. There are wide variations in the quality of their family relationships, and they will continue to follow varying paths in the pursuit of diverse life styles.

The leaders of the women's movement are expressing deep concern about what they call its fall out on young working women. The professional literature and the media are worrying about the pressures on young women, and about the effects of their working on their young children and on their marriages. If the young women are experiencing strain, so too are the middle aged, though the specifics of their situation are different. Most conceptualizations of the family life cycle take note of changing roles over time, and the normal developmental aspects of those roles shift. In general, the roles played in the social definitions of appropriate behaviors in those roles are in synchrony with the emotional and the physiologic developments and capacities. The child bearing years, for example, are those in which young adults not only may wish for children and have reproductive capacity, but have energy levels that are commensurate with the care needs of young children. When the role of caregiver to an impaired very old person must be assumed in late middle age or in early old age, the demands of that role may not be synchronous with the physiologic, psychologic and emotional capacities of the caregivers.

By contrast, with the gradual reduction of the young child's dependency, the dependency of impaired older persons augers continuing or increasing dependency. The physical care of an extremely impaired older person is different and more difficult than in the care of the young child. For the adult child whose own beginning processes of aging require major adaptation, the parents' dependency may make too great a demand on the supply of psychic and physical energy. When the very old person is extremely impaired, and the capacity of the aging child to give care is not equal to the task, the role of caregiver is not a normal developmental stage of life. To focus on the very old individual's needs to the exclusion of the caregivers' needs disregards reality and places yet an added burden of guilt and stress on the individual or the family who fails.

What are the prospects and the solutions? If we know little about how the patterns of the care of the aged are changing now, we know even less about the future. If middle aged working women are less available, will the old receive less family care than in the past—less than they need? Will tradition live and their demonstrated commitment operate so that women in the middle attempt to take on the work role without reducing their parent care activities? What will be the physical and mental health effects on their elderly relatives, on the women themselves, and on their husbands and their children? Will parent care activities be reallocated among various members of the family? And what will be the social and economic costs to society?

When the women's movement began, some people made the naive assumption that the goal was for women to gain equality by broadening the scope of their activities in the world of men. But as Weithorn (1975) has pointed out, that notion yielded to the realization that change must occur not only in women's roles, but in men's roles as well. Realignment of male-female relationships in the divison of labor, she argues, should use the concept of equitable rather than equal—this is, not equal sharing of the same responsibilities but fair sharing of the total load. Looking at women's roles in historical and crosscultural prospectives, Weithorn wrote, "Now that strength is no longer a requisite for survival, pregnancy no longer a consequence of sexual activity, and the infant no longer dependent on the mother's breasts, women are demanding a revised contract, one more adapted to survival in a contemporary society."

A revised concept between young men and young women has not yet been drawn up or ratified. Many men have supported the women's movement and have made genuine efforts to change their own life styles. Many accept their wives' working as an economic necessity. In the light of evidence about the lack of significant sharing between young men and women, young men of young couples, the expectation that the solution lies in the sharing of parent care between husbands and wives, or between brothers and sisters, is naive. At best, such sharing would provide only a partial answer to the problem. The combination of women at work, and the additional demand for parent care, means not a redistribution of traditional responsibilities of both sexes, but a reallocation of both former and additional responsibilities.

It is clear that the mix of formal and informal social support must change. Social policy must move vigorously to implement the call of professionals for a family oriented social policy to support the informal support system. The myth of family alienation in all its guises continues to pose a serious barrier to such an agenda for aging families. Policies and services to help young women are inadequate but are improving and the need for them is becoming more recognized and acceptable. Services and policies such as relief, child care, and day care are improving. Many forms of help for young mothers have always been elements of our social institutions: babysitters, nursery school, visits from grandma to babysit so mom can have an afternoon off, and so on. Yet social attitudes toward providing services to help families with their old are often sanctimonious and judgmental.

The question is at what point does the public and professional expectation of filial responsibility become social irresponsibility? The revised contract that is needed cannot be solely between men and women. Our values require reexamination so that the contract can be negotiated between the family as a whole and the health social support system that only social policy can create, and that only health and social practitioners can implement. Otherwise, the most caring, sophisticated, and meticulous geriatric medical care will be sabotaged.

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Future Directions in Reimbursements for Medical Services for the Elderly Residing in the Community. Who Pays?

Honorable Mario Biaggi, Chairman,
Subcommittee on Human Services House Select Committee on Aging

Editor's Note: Representative Biaggi's talk is printed intact. Ironically, he was unable to attend the Brookdale Conference on Geriatrics because of a pending legislative vote on a geriatrics issue the same day.

It is an honor to be present at the Fourth Annual Brookdale Medical Conference on Geriatrics at The Mount Sinai Medical Center. Since my election to Congress in 1968 and up to the present, I have maintained a special interest in the well-being of our elderly citizens. As an original member of the House Select Committee on Aging and Chairman of its Subcommittee on Human Services, I have witnessed the Committee's emergence as one of the strongest and most effective advocates for older Americans. In this capacity I have had the privilege of working on key legislation designed to address the major health and social welfare needs of the elderly. This task has been both a gratifying and difficult one which will continue to grow in importance with the attendant numbers of Americans over the age of 65.

The topic of discussion this afternoon—"Future Directions in Reimbursements for Medical Services for the Elderly Residing in the Community. Who Pays?"—is a critically important one which will continue to demand greater attention from legislators and policy makers throughout this nation, particularly in the latter years of this century. The urgent need to re-examine our current policies toward long term health care for the elderly hinges upon two factors: the growing numbers of older Americans and the dramatic increases in the cost of health care.

The "baby-boom" of the 1950's is now maturing into the "senior-boom" so that by the year 2030, there will be 55 million elderly—or more than twice the 24 million there are today. Not only is our nation as a whole becoming older, but people are living longer than ever before. These longevity gains are significant because, among the senior population, the fastest growing segment is the group of 75-84 year olds. Known as the frail elderly, this group will increase by 50 percent between 1978 and the year 2000. They are generally the most functionally dependent and therefore require the most extensive health care services of the total population.

Accompanying this demographic revolution is the steady escalation in national health care expenditures: Between 1965 and 1978, the overall cost of health care grew at a compounded annual rate of 12.2 percent while the Gross National Product trailed at a growth rate of 9.0 percent. In 1978 these expenditures totaled $192 billion; they are projected to reach $245 billion in 1980; $438 billion in 1985; and $785 billion in 1990.

Moreover, before fiscal year 1967, the private sector had been the primary source of health care financing. Since the inception of the Medicare and Medicaid programs, however, the government has assumed an increasingly larger share of this responsibility. In 1966, the public sector financed 25 percent of all health care expenditures; today the bill has climbed to 40 percent.

The combined force of these trends—the growing numbers of elderly and unchecked health care costs—have significant bearing on the design of our nation's long term health care system.

Presently, the health programs which contribute the major portion of public funding for the elderly are Medicare and Medicaid. In 1977, the total per capita personal health care outlay for older Americans was $1,745. Of this amount, Medicare paid $715 or 41 percent and Medicaid paid $291 or 16.7 percent. There is no question that both programs have made substantial contributions to the improved health status of millions of Americans. However, with respect to the major health care needs of the elderly, which are chronic in nature, unless a shift toward inhome and community care is achieved soon, many elderly will be left without care in their "golden years."

This ominous forecast stems from the fact that these important programs offer minimal support for the long term care needs of the chronically impaired. Both Medicare and Medicaid are oriented toward the treatment and cure of episodic disease rather than emphasizing preventive and maintenance care for those with chronic disorders. A closer look at these programs reveals numerous disincentives to community-based care, including a decided bias toward institutionalization.

The Medicare program was designed to assist the elderly with high hospital and surgical costs. The home health benefits are limited and generally tied to a hospital admission or the need for skilled care. Benefits do not extend to services related to assistance in activities of daily living unless they are provided in conjunction with some form of skilled care. In 1977, Medicare paid for 41 percent of elderly medical bills and 56 percent of all physicians expenses. Only three percent of all Medicare funds, however, went to finance nursing home costs. Other vital health services such as medicines, eyeglasses, dental care, hearing aids, and home health care were purchased primarily through private funds.

Medicaid, on the other hand, has evolved into the major provider of long term care for the elderly. This has been achieved mainly through institutional instead of inhome or community-based care. Currently, 41 percent of the Medicaid dollar pays for nursing home costs which predominantly support low income elderly residents. Since only six percent of those in the Medicaid program utilize nursing home services, this type of arrangement in long term care is a very costly one which benefits a minority. Only one percent of Medicaid dollars pays for community-based care, thus leaving the majority of needy elderly with inadequate means to secure care in the home.

The Medicaid program, or the main vehicle for financing and delivering long term care in this country, is presently designed to favor institutionalization over home care for the chronically ill elderly. While nursing home coverage is extensive, the availability of home health services vary markedly from state to state in amount and duration. Since the chronically ill usually have a multitude of needs, including social services needs, it is often very difficult to obtain the appropriate mix of services to enable an elderly individual to function independently in the community. Studies have shown that elderly persons will simply forego the home care that they need if, as is often the case, they cannot afford the costly services. Hearings conducted by the House Select Committee on Aging have revealed that up to 20 percent of all nursing home residents are inappropriately placed despite their preference to live in their own homes. Many are institutionalized who do not have major medical problems because of the lack of community supports. The presence or absence of family members to care for an elderly relative is often a critical determinant in the decision to institutionalize. Yet, those families who assume such a responsibility can expect to receive little or no financial or service assistance. Moreover, individuals who are not eligible for Medicaid when living in the community may qualify once in a nursing home because of a double set of income criteria which allows a more liberal application in an institution. These Medicaid policies coupled with the problems inherent in securing community-based long term care results in otherwise avoidable nursing home admissions.

The traditional medical focus on diagnosing and treating disease instead of functional status is another factor in the institutionalization of the elderly. Physicians have been trained to cure disease rather than detect the debilitating disorders which affect the chronically ill. Instead of treatment in a nursing home or hospital, an elderly person may actually need a package of social and health services to enable him to live an independent life. Yet the medical orientation toward acute care combined with the paucity of training in the treatment of the chronically ill elderly serve to maintain the bias toward institutional care.

The field of geriatric medicine has remained neglected despite the evidence that the chronically ill require a different approach to treatment. As of 1978, only 44 of the 120 United States medical schools offered electives in geriatric medicine and only a handful of the 44 actually required students to attend classes in geriatric medicine. The competence of geriatric health care personnel, though, is vital to the success of any health delivery system. Untrained personnel are more likely to misdiagnose and prescribe inaccurate treatment and service delivery by untrained persons is more likely to be haphazard and costly.

To summarize, the major public programs

which finance medical services for the elderly offer little assistance for inhome and community-based services. The major thrust of programs such as Medicare and Medicaid is toward the care of acute short-term illness. As a result, many elderly who may not need the costly and intensive medical services are nevertheless placed in nursing homes in order to receive the appropriate mix of services. Initial needs assessments are often performed by physicians or other medical personnel who are not trained to identify the types of assistance which could allow the individual to remain in the community. Finally, the array of community-based services which benefit the chronically impaired elderly are fragmented into so many different federal, state, and local programs, each with their own regulations, reimbursement methods, and overlapping constituencies that it requires a herculean effort on the part of the lay person to successfully arrange for a comprehensive package of services needed.

I have outlined some of the problems in our current long term health care system for the low income elderly. I would like to turn now to the reforms which have been suggested in the 96th Congress and which, in several instances, will soon be implemented to make the health care system more responsive to the largely unmet needs of the chronically impaired elderly.

The Omnibus Reconciliation Act of 1980, which was signed by President Carter on December 5, contains a number of significant changes in the Medicare program. With respect to home health services, this legislation has provided for the following: 1) Medicare coverage for an unlimited number of home health visits; 2) Elimination of the three-day prior hospitalization stay requirement under Part A (This removes the previous incentive for the unnecessary hospitalization of Part A beneficiaries as a means of obtaining access to home health benefits and thus helps to avoid premature and inappropriate nursing home placement); 3) Elimination of the $60.00 deductible for home health benefits under Part B (This eliminates the remaining patient cost-sharing on home health services and encourages their use); and 4) Includes the need for occupational therapy as a qualifying criterion for home health benefits.

With respect to outpatient surgery, The Reconciliation Act provides Medicare reimbursement for certain surgical procedures which are frequently performed on a hospital inpatient basis but can be safely performed in an ambulatory surgical center or doctor's office.

Financial arrangements have important associations with service utilization and these provisions for Medicare reimbursement should encourage the use of more home health services and outpatient surgery.

The Medicaid Community Care Act of 1980. I am a cosponsor of the Medicaid Community Care Act of 1980 which would remove the bias toward institutionalization by increasing the Federal contribution match for community-based services by 25 percent for those individuals at risk of institutionalization. States wishing to participate in the program would be required to develop and implement a state community care plan which would include the following provisions:

* A comprehensive medical and social assessment of all individuals at risk of being institutionalized.

* Expansion of home and community-based services. The cost of such services, not to exceed state nursing home care rates, would be governed by limits established by the Secretary of HHS.

* Coordination of other medical, human and social community based services with the Medicaid program.

This bill, which I plan to support vigorously in the 97th Congress, would allow the vast majority of chronically impaired elderly to live at home and also receive the mix of human, social, and medical services necessary for daily living outside of an institution.

The National Long Term Care Demonstration Program. The Department of Health and Human Services has undertaken a demonstration project to test new systems at the state and local level to organize and manage the delivery of long term care services. Thus far, 27 states have been awarded $12 million to establish programs in which public and private agencies will join forces to assure that those in need receive the appropriate care in the most efficient way. Each project will have the responsibility of performing a comprehensive and multidisciplinary assessment of client needs; developing a plan of care tailored to the individual; monitoring the implementation of the care plan to see that the appropriate mix of services are delivered; and follow up to assure that services were provided satisfactorily. The ultimate goal of the program is to improve the quality, availability, and accessability of long term care. Toward this end, data gathered at demonstration sites will be used to plan and coordinate community systems.

Obviously, there are no easy solutions for the effective delivery of long term care. The challenges awaiting us far outstrip the proposals, reforms, and demonstration projects currently being undertaken. It is evident however, that if we are to be successful in establishing an effective long term care policy we must be prepared to commit more in the way of resources and manpower. Elements involved in such a strategy to benefit at-risk populations such as the aged, include the expansion of community-based programs, Health Maintenance Organizations, and a greater emphasis on preventive and primary care. Similarly important is the growing need for the public and private sectors to work in closer partnership to develop cost-effective measures that will lay the foundation for financial discipline in the health care industry.

Before I conclude, I would like to say a word about the benefits of foresighted planning. I do not believe that there is a person in this room who would dispute the fact that it is an important factor in any policy making endeavor. From my experience however, foresighted planning is usually the exception rather than the rule. Nonetheless, and in an effort to change this, last May I issued a report entitled "Future Directions For Aging Policy: A Human Service Model" which discusses the impact of our aging society in a host of critical areas. It suggests a new approach to the delivery of human services to the elderly and proposes a long range policy to address the future needs of America's aged population. This document was written to raise questions and stimulate new approaches to old problems. I believe that similar future studies on issues such as long term care would assist professionals and policy makers to make the appropriate decisions for tomorrows programs.

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Panel Discussion

Panel Members: Samuel K. Elster, M.D., Chairman; Leslie S. Libow, M.D., Reubin Andres, M.D., James F. Holland, M.D., Carl Eisdorfer, M.D., Ethel Shanas, Ph.D., and Elaine M. Brody, M.S.W.

DR. ELSTER: Panelists, although some of the questions gathered from the audience are directed to a particular member, please feel free to respond.

Dr. Andres, if you have a patient with elevated uric acid, elevated triglycerides and normal glucose tolerance, would you avoid the use of thiazides?

DR. ANDRES: I must say that when practical problems of patient care come up, it has been a very long time since I have practiced medicine. When a clinical question comes up, I put on my physiologist hat; when a physiology questions comes up I put on a clinical hat. I really don't know the relationship between thiazides and triglycerides. Do thiazides elevate triglyceride levels, Dr. Libow?

DR. LIBOW: No, but could you repeat the questions?

DR. ELSTER: In patients with elevated uric acid, elevated triglycerides, and normal glucose tolerance, would you not use thiazides?

DR. ANDRES: The implication of the question is that the patient might be what we used to call a prediabetic, or a potential diabetic, because of the association between the elevation of the substances. In diabetes, the use of thiazides might bring out a potential case. Since we are all in one way or another potential diabetics, I don't think we should limit the use of therapeutic agents on those grounds. To answer the question, yes. If there is a good indication for the use of thiazides, use them. Follow the patient periodically, depending on other characteristics of the subject with glucose tests.

DR. LIBOW: If we are talking about older patients and if there is a clear indication, like hypertension or congestive failure, I totally agree with Dr. Andres. You cannot worry about the theoretical problems with even worsening the uric acid, or bringing on the diabetes. We use the medication. If there is a uric acid problem that develops as worsening problem, that can be dealt with by inhibiting agents. This is a different question, however, if you are talking about a 30-year old.

DR. ELSTER: As a practicing cardiologist who uses a good deal of thiazides, I also agree. But you can be certain that ten years from now when someone does a study, we will all be proved wrong. Use the drug as is needed. Don't use your hydrochlorithiazide if you are treating something that does not require treatment. You can certainly take care of the side effects as long as you can anticipate what side effects occur.

The next questions is to Dr. Libow. When is a physician or a medical student being too truthful with patients, especially geriatric patients? Would each member of the panel respond, substituting for the word student the appropriate health professional.

DR. LIBOW: I alluded to it briefly in one of the 12 items I highlighted earlier. I believe there is a point when one is too truthful in selected cases. I am worried about what appears to be almost a rule now that people seem to be bringing to the clinical situation. It is certainly true in medical schools, and it may be true in other health care schools in general.

Since the end of life is not the happiest message, it seems that today's death and dying trend has distorted that into a truth-telling mechanism. We think it is an obligation to rush to patients and clearly share with them their diagnoses so that they can go and do all the things they might wish, like praying and crying. This is true and important for some, but not for everyone. We must be selective. If we do not know how to be selective, we must turn to more experienced people who can at least assist us in deciding who can deal with the information and who cannot.

MRS. BRODY: I assume the question was asked about elderly patients. I would say in response that elderly patients are not different in this respect from the younger population. They still have the same right of decision-making, and most of them are still intact cognitively. The same kind of sensitivity needs to be applied in working with older people as with younger people and children. I agree with Dr. Libow that truth telling for the sake of truth telling, forcing it down their throats whether they are ready to hear it or not, is not always appropriate. The sensitive health professional listens to what the patient is ready to hear, and the point at which they are ready to hear it. But certainly, do not deny the truth.

DR. ANDRES: I really don't know if I have any deep insights to offer except this. This is a marvelous age of computers and of scientific medicine. We can feed information into a computer and get diagnoses out with probabilities of accuracy and recommended therapeutic regimens. I don't believe in this case that a computer would help very much. This then is part of the art of medicine. There is no simple formula to answer that question. As an adult, and a sensible person, I would echo what Dr. Libow said. If you don't know what to do, you'd better talk to somebody else who is older and wise.

DR. SHANAS: This question recalls to me a comment made many years ago when a certain professor and I studied whether older people thought much about death and dying. One woman in her 70s, a dietitian in a girl's school in Philadelphia, answered "death does not concern me. I know it is inevitable. It is living that is my problem." The physician should approach the patient from that point of view.

DR. ELSTER: Dr. Libow mentioned how we are training our medical students to reveal the truth and, indeed, we have the patient's bill of rights, in which the patient is entitled to the truth. It is important sometimes to couch things so that information can be imparted to the patient, but not overwhelm and, therefore, produce an acute depression. The patient is entitled to know the facts. It is the way facts are presented to him that sometimes can alter a situation. As Dr. Holland said, there is no such thing as a fatal cancer. It is precurable. Present factually, but with a little kindness. As facts are being portrayed, which is really what Dr. Libow alluded to, sometimes a patient subjectively is not capable of receiving, digesting, and understanding the information without explanation. Now a question for Mrs. Brody.

Do you know any books that would best help the lay person as a guide in taking care of the parent?

MRS. BRODY: There have been a number of books written for families from different perspectives. One of them is called *You and Your Aging Parent,* written by Barbara Silverstone. There is a chapter in my book on families. Another one was recently put out. If the person who asked the question would give me their name and address, I will send them a bibliography.

I would like to take the liberty of making one more comment in response to the previous question. I think issues come up which indicate that we think of old people as being apart from the rest of the human race. We begin to feel as though there are many special considerations. Please, think and treat older people as people. Just because they are old does not mean that we have to make decisions for them. The other day, a man called me who was terribly upset because he and his sister were fighting about whether or not their father should be institutionalized. It was becoming a bitter family battle, even though at 92 the old man's mental capacities were intact. He was capable of decision making. They were really taken aback when I asked what the father himself wanted to do. Let's not wipe out the older people or think of them as different from younger people. You are all going to be old some day, hard as it may be to believe it. Close your eyes for a minute and picture yourself as a 90-year-old person. It almost cannot be done.

DR. LIBOW: In my experience with our own program, it seems that older people receive catastrophic news as well if not better than middle aged and young people. Yet the question comes up, when is there too much truth? The question implies how could there be too much truth telling when the opposite might be paternalistic and too much taking charge by the physician.

I want to share a story with you. It actually involves one of the outstanding people in social services at Mount Sinai. Hannah Lipsky and I were involved with a patient years ago, named Maria. She had disseminated cancer of the breast and was pretty sick. Nobody had discussed her diagnosis with her directly. She was a Cuban immigrant and spoke perfect English. Her family lived in Florida and she was in New York.

I had been reading a lot about death and dying. I thought I knew the literature pretty well. I had good experience in my work in Geriatrics and had become familiar with Cecily Saunders' work. I was learning a lot from her, and came back to my work more inspired than ever.

Maria sat on the edge of her bed everyday when we were on rounds. Although we had come to know Maria quite well, we still never discussed her diagnosis with her. She knew something not so good was going on, maybe she even knew the diagnosis. Nevertheless, I didn't sit down with her nor did anyone else on the team. I told Maria we were having more trouble with her anemia than we anticipated. Her eyes started bulging. I don't know why I said it that way. I don't remember her response, but that night she had an acute psychotic episode. She was wild and unmanageable. We could not communicate with her. She was seen by psychiatrists, social services and the rest of the medical staff. She was on sedating drugs for about four days. I felt extremely guilty, and a lot of people were mad at me. It was one of the worst experiences I ever had at that point, ten years ago.

The end of the story is a little better. Maria came out of the depression and was able to communicate and say "I think I have cancer." We talked about it. She saw a lot of people, and her family came up from Florida. She experienced the kind of things we think we would like to experience if we got into that kind of trouble. The reason I share this story with you is 1) so we can hear more about this from the panelists, and 2) dangers are never that clear. I did not think at all that a simple and I thought gently handled communication would produce such trauma. We are really dealing with some pretty difficult situations and need to be extremely humble and cautious.

DR. ELSTER: Perhaps Dr. Holland would like to respond to what we are talking about. He is faced with patients with cancer, many of them are subcurable, and others are precurable. Dr. Holland, how do you handle giving information and do you ever withhold it?

DR. HOLLAND: I am very humble. I think that the worst thing that happens to patients is for someone blatantly to lie to them. It clearly is an arrogation of the truth if someone, a spouse possibly, decides what the person shall or shall not know. It is a delusion of the patient, and a delusion of the spouse and a delusion of the physician that one can withhold this kind of information. When you blatantly, deliberately lie, you cheapen any of the health profession.

That is not to say one has to be brutal in enforcing the truth on someone in a pathologist's terms. You have cancer that is eating away at you. Your survival will be limited, and we certainly expect that you are going to die like everybody else is going to die. On the other hand, to say no, it is benign, denies the person a chance to adapt to something that they will come to know anyway. Frequently, there is the very subtle wondering of why the patient is making conversation impossible. The saying that the same bricks make hovels as well as temples applies here. It depends on how you arrange the facts. The opportunity to adjust to a curtailed life, or to prepare oneself for the beauty of death—which in our culture has very little of what it has in other cultures—is important. I don't lie to people. Yet I don't necessarily tell them, yes you are hopelessly ill, because you are terminal. I don't believe that is so. All of us are terminally ill, we are all going to die. This is no surprise. Particularly among the elderly, I think there is a great deal of accomodation and acceptance of a noble and dignified way to die. It is wrong to deny someone that opportunity. For example, there are particular religious concepts that I think are associated with authoritarian arrogation of responsibility to the religious leader as to who will or won't know something. I find that particularly offensive. I don't think that it is the duty of an outsider to enter into the spouse relationship or the parent-child relationship, or the patient-doctor relationship. By and large, I believe truth is a good policy. Gentle truth is a good policy and may be done offering anything that is not asked for. Perhaps the best exponent of this was Oliver Wendell Holmes, who said that a patient has no more right to all the truth than to all the medicine in my saddlebag.

When you tell a gentle truth, a patient may be satisfied with that amount of truth. The patient may ask how long am I going to live or am I going to have pain. Very often, patients ask what are we going to do now. Then the physician can give an upbeat answer within the limits of the truth. But to promise cure, or to promise that the cancer has all been removed or to promise that it is benign, or to otherwise dilute information, I think cheapens medicine and cheapens the doctor-patient relationship.

DR. ELSTER: Do we have any other responses from the panel?

DR. LIBOW: Well, a brief response. I don't believe there is death with dignity. I really don't subscribe to that concept. It seems to be a false promise. There is only life with dignity.

DR. HOLLAND: I would like to answer that. I agree completely that one wants to have life with dignity. But there is a time to die and some patients, who are knowledgeable of the biologic preparations to their own suffering and to their family's distress, are denied death with dignity. There are people who say to me all the time, I am ready. I had a good life. I don't want any more treatment, I would rather go home. That is death with dignity. The actual act of ceasing respiration is not death. Death is the preparation for leaving loved ones behind. The person who is dying is going to suffer only once on that road. He may not suffer at all. He may be suffering terribly to stay alive. Those who love their families recognize that their own departure is going to cause pain and suffering. There is dignity in knowing that they have made their contribution and have helped others along.

Maybe we have difficulty discussing what is death. Death is the entire process of knowing that the end is here, and resigning to it. Most people can.

DR. ELSTER: As a psychiatrist, Dr. Eisdorfer, do you have some feelings in this matter?

DR. EISDORFER: We have a semantic problem here. The semantics can be as confusing as they are enlightening. While dying isn't all that dignified, it can be just as horrible as the notion of a biologic specimen. We have seen this kind of problem in the past and don't want to perpetuate it.

I first learned about death with dignity when I was an intern in medicine at Duke. I was called on to attend the father of a physician who was a close colleague of my attending. I thought I was brilliant, having just won the Old Buffalo Award, and was the hottest intern on the ward. I was going to keep this poor 80-some-odd-year-old gentleman alive despite everybody. It took an act of considerable courage on the part of my attending, who took me aside with the physician/son of this sick man, to tell me what not to do. I have always felt that was as important in my medical education as all the things I had learned to do so brilliantly.

There is a time to die, and there are places to die. There are right and wrong ways to help that process. We cannot push people to death nor can we in our limited wisdom, deny them a death. On the other hand, this is not a decision to make alone, one must make it again, not just as a physician, but as a mediator for the family, the patient, or anyone else.

The doctor who taught me the wrong thing about senility taught me the right thing about dying with dignity. That was Gene Stead, who published in the *Archives of Internal Medicine* when Ward Varganeve was editor, how he wanted to be taken care of, per chance, he collapsed on the floor of the Massachusetts General Hospital where his daughter was a resident. He gave very strict instructions to the field of medicine as to how he wanted to be allowed to die. I think that says a lot.

Getting back to the physician/son example: here was a role reversal. Here was a physician who had to make decisions about his father who was no longer capable of making decisions and I thought it was legitimate to relate to him. He had then become the spokesperson for his family and the family had made a decision. He and my attending were saying to me in very clear terms, how I was to act. I learned a lot. I think that was one of the important insights I developed as a clinical physician.

DR. HOLLAND: I don't want my remarks to be interpreted as anything against an activist approach, when first seeing a patient. I don't know about Dr. Stead stretching on the floor of Massachusetts General, but it sounds to me like someone who might be a little anxious. If I have to stretch out in a sudden attack of something, I would hope I would be in the lobby of Mass General or Mount Sinai rather than on the street like a common catastrophe. It just seems to me that every patient should be looked at as potentially saveable when first seen. It is only upon establishing the inevitability of death which is there for all of us that we then decide the time span for different patients. Different cancers are very different. Some patients will live with their cancer, like they live with their diabetes, or with their neurologic disease, and others will be on a much more rapid descent. It is in the terminal stages of a rapid descent of any disease, not just cancer, that I think one should temper mercy and common sense with the heroics of being an intern.

DR. ELSTER: Here is another point. The quality of life that was enjoyed by that patient prior to that episode was taken into consideration. Obviously, in emergency situations with somebody who is functioning well, irrespective of age, every effort at resuscitation must be made.

On the other hand, if somebody is in the last stages of a terminal illness, what I hear being said here is that we need a little medical wisdom as to when to pursue beyond the pale.

MRS. BRODY: Also, there aren't any rigid rules. People are different. Even though we can have certain principles about what we believe in about truth telling, we have to be sensitive to the many social differences in human beings. We have to be aware also of rigid procedures such as those of Elizabeth Kubler Ross.

She sensitized us to the whole process of dying. You cannot apply any one technique rigidly. In her six stages of death and dying, what do you do if somebody skips a step, for example?

DR. EISDORFER: You go back.

MRS. BRODY: I mean, you just can't apply anything that rigidly. You have to use your skills, your understanding of people and your sensitivity to what they are ready to hear.

DR. EISDORFER: I agree with the approach and not telling the patients anything they are not prepared to hear. However, based on a specific clinical experience that I had, the physician can significantly alter the patient's interest in talking or listening by something as simple as whether or not you sit down when you come into the patient's room.

I saw a patient being told what was wrong with him in the hallway of his room, the standard medical room which has a closet on one side, the shared bathroom on the other. The physician who never got past the door of the bathroom and could barely see the patient's head, was telling the patient, not directly, what he had. The patient who had come in for a thoracic aneurysm, which turned out to be cancer of the lung, was being told "we are not going to operate, but you are going to get radiation therapy beginning tomorrow." The patient happened to be a very bright lawyer and obviously understood that if he were suddenly being switched from surgery to radiation therapy, what the implications were. The physician turned around and left.

The patient was my father-in-law and I had to literally run down the hall to catch the doctor to find out what was going on because nobody knew. That is the abuse of medical privilege that I think we are really concerned with. Physicians who sit down and are willing to discuss with the patient will immediately learn what the patient wants to know. If you have to lie, you're in trouble.

DR. ELSTER: I would like to go on, Dr. Andres, to a medical question. It deals with the diabetic 70 years or older. What is acceptable blood sugar control and is age a factor in control and in treatment. Do we treat the number, or do we change the morbidity and mortality in the newly diagnosed 70-year-old diabetic by keeping the sugar at a range described as normal?

DR. ANDRES: The degree of control in the diabetic is a very big controversy in internal medicine. The evidence now seems to be moving back to a tighter control. There is evidence of reversibility, and what might be called secondary changes of diabetes. Some of this evidence is coming from what is still experimental procedure, the insulin pump, which gives continuous insulin infusions, supplemented by insulin, programmed for mean intake. Great improvements in blood sugar level, in fact, normalization of blood sugar, have been maintained for long periods of time, even months. There is evidence of reversibility of some of the complications. The trend now is definately back to tighter control.

DR. ELSTER: Do you apply that as well to the elderly?

DR. ANDRES: Yes, within the limits of avoiding hypoglycemia, which is much more dangerous in the older person than the younger.

DR. LIBOW: Most of the successes with the insulin pump are probably most clearly related to the classic juvenile onset diabetic. Although the pump has been used with all age groups, for the first time we have some data to suggest that there is some reversibility to some of the complications of diabetes. This is a dramatic breakthrough, but I would not, extrapolate to the mass of older diabetics truly defined, even with the strictest criteria.

I would not extrapolate and make a major push for tight control of the diabetic who is being given oral medications because of the other changes, such as hypoglycemia, possible vascular complications, until we have more information. I would not be in favor of treating older adults' onset diabetics with vigorous oral treatment.

DR. ELSTER: How could medical directors of long term facilities upgrade their skills and knowledge through courses, and upgrade their institutions?

MRS. BRODY: There are courses that are given. I am not as familiar with the New York scene as I am with the Philadelphia scene. We give courses at the Philadelphia Geriatrics Center. There is a very highly developed facility in New York that has been giving courses for many many years to all kinds of personnel (medical directors, administrators, social workers) of long term facilities. It is the Frederick Zeman Center at the Jewish Home and Hospital for the Aged, where you can get credit for the courses.

DR. ELSTER: Dr. Holland, is there any age at which you would modify your recommendations for chemotherapy for cancer?

DR. HOLLAND: At the extremes of life, chemotherapy is difficult. In children under the age of one, the diseases are more malignant and chemotherapy is difficult. In the other extreme of life when normal required organ systems are beginning to fail, such as renal function, marrow function, cardiac function, cerebral function, there are again difficulties in using chemotherapy. The choice of agents must be tempered and, at times, the type of therapies. If cure is attainable, cure is worthwhile trying. If cure is not attainable, palliation means palliation. It does not necessarily mean giving drugs. It means reserving for the maximum time possible a high quality existence. Not just life under circumstances that are unhappy and intolerable; but life that has ambulation and self-reliance and, if possible, occupation. The patient does modify the choice of treatment, but not the choice of the aim. There are certain tumors that in certain streams of life have unique treatment characteristics. The older the woman gets, the more likely her breast cancer is to be dependent upon or responsive to hormonal treatment. This becomes a more important agent to those in their 70s and 80s, than it is to those in the 40s and 50s, but I think that general proposition is correct.

DR. ELSTER: Dr. Libow, you mentioned the lonely and searching physician, the physician who must make a decision without knowledge of the patient, or a family physician, but you gave no guidelines. Are there any you could offer? Perhaps other members of the panel might like to respond?

DR. LIBOW: This has to do with the patient for whom we don't have any insight, the patient without a penultimate will, without a living will, and without going through the arduous task of going to court. If you are the physician who knows the patient for a long period of time, you have to make a sensitive guess as to the patient's wishes, the patient's style of life. If you don't know the patient, you have very little right to make a decision for nontreatment. If you are the resident physician at night, coming to an emergency and a patient appears to be hopeless, but you know very little about the case, or you see a diagnosis on the chart of organic mental syndrome, and you say to yourself, I am not going to treat, I think you have taken more responsibility than should be granted by medical license. If you know the patient for many years, or for a period of time, you still are taking some license. But maybe its appropriate and it is better than going to court.

MRS. BRODY: This is not responsive to the question, but I have to express something that has been worrying me for the past half hour. Almost all of the questions have been asked with very few exceptions, about the process of death and dying. This makes me wonder whether the people in the audience are feeling that aging is synonymous with death and dying. If you do, please let me assure you that it is not. Many people live thirty and even forty years beyond that magic age of 55. Many of them live comfortably, are well, don't need help from anybody and are intact. There are a lot of questions about living in old age that are relevant here. It is not synonymous and exclusive to the process of dying.

DR. ELSTER: I am glad you brought that up because I would agree that in older lives, we must not only consider death, we must consider living. A question, for Mrs. Brody. You have pointed out the problems of the middle aged woman and her aging parents. Do you have a suggestion for the solution?

MRS. BRODY: I think that social policy must develop to support the efforts of the family. We have no social policy at this point. The noises are made on the federal level, but nothing is being implemented. I could describe a laundry list of the kinds of services that are needed. One, for example almost everyone could relate to is what is called respite care, or temporary care. Today, if a family has been under the strain of taking care of an older person, with Alzheimer's Disease, for a year, and needs a vacation or if there is an emergency in the family, respite care is not reimburseable anywhere in the United States. I know many physicians who are compassionate and will often use a hospital as a means of respite. But this is a very costly service.

There is a tremendous inventory of services that we could have as in-home services, the service of boarder living arrangements, or day care which is now universally available. Social policies must move to begin to develop these services or we will create a whole new group at risk. We have done it already. They are at risk of mental-physical breakdown.

DR. SHANAS: There are many things that could be done, but they involve some statement of national priorities, some commitment of national funds. Until such a commitment is made, I am afraid we just have to thrash around, as we have been doing with small programs with demonstration funding. The future is not bright for the 70-year-old adult child with a 90-year-old parent.

MRS. BRODY: This relates to a professional attitude, as well as a social policy. I don't think health professionals are accustomed to giving the family instructions or inquiring as to the family's capacity when they are about to discharge an elderly patient.

Is the wife going to be able to turn this heavy man in bed, or to get him in and out of the bathtub? Do the children live nearby? How old are they? What are their other responsibilities?

There has to be much more consciousness raising about the entire family and its needs. The doctor has to establish a much firmer partnership with the social work practitioner whose responsibility it is to link into what services are available. We need a change in professional attitude as well as new social policy advances.

DR. EISDORFER: There is no question that we need very striking differences in social policy concerning the family's role in caring. Current policy is based on misinformation. Our society has that psychological, social dumping syndrome, not the abnormal variety. Being a realist, I am aware of the effects the November 1980 elections will have. The notion of developing certain changes in social policy in a direction that, I think we all believe would ultimately be, if not cost saving, but an advance of human dignity, is probably unlikely. We don't have to stay with national social policy, however. Local groups can make a profound difference.

For me, a fascinating adventure over the last six years has been helping with the development of a local support, family support group which has now gone national. I mentioned Alzheimer's Disease and Related Disorders Society which, in our area, was originally founded as a group called ASSIST. ASSIST started out with five families, five years ago. There are now 500 families. They provide their own sort of respite care. Altogether, they provide about 25 different services. True, it's a shoestring operation. It is also true that if you magnify this we could get something going.

What we need is social attitude change. We have to get away from the senility notion. We have to get away from what I, too, call distinctive death associated with aging. None of us know when the patient is going to die. To think that everybody over 65 is on death row and, to respond accordingly, is to perpetuate precisely the kind of problem that we have been having for centuries. Very candidly, with our changing demography we can no longer afford the luxury of ignoring that change. We are going to have to start shifting social attitudes, medical attitudes and public opinion about where older people fit in our society. Otherwise, we are doomed to live the role that we established for everybody else.

DR. ELSTER: Dr. Libow, what, if any, are the Judeo-Christian implications of the penultimate will?

Dr. LIBOW: I am going to pass on some of the profound Judeo-Christian implications. I really was attempting to highlight and, in some cases, share with you my approaches from the point of view of a clinician not an ethicist or philosopher. I could handle the question better privately. I will try to respond with one point, though. Being responsible for one's actions, or the actions affecting one's family certainly would be in the best Judeo-Christian vogue. I think that penultimate wills are the ultimate in responsibility.

MRS. BRODY: I think we ought to be able to ask questions, too, Years ago, a sociologist named David Sudlow did a study in which he wrote a profound statement. He found that when a patient was old, the ambulance drivers drove more slowly, the driver didn't lean on the horn, and the team didn't mobilize as quickly. This morning in Dr. Libow's presentation, he talked about the kinds of triage that goes on in the Coronary Care Unit, where a limited supply of beds has to be allocated more efficiently. He suggested criteria for the selection of patients who should be given the advantage of the very sophisticated procedures. My question is, why didn't he suggest that there be adequate facilities so that a physician didn't have to make choices as to which individuals should receive treatment?

DR. LIBOW: That is a super question. I did try to say that I find that many of us in the health care system, especially those of us with some modest administrative or public responsibilities, seem to accept the urging from the government that we quickly turn into cost effective roles. I warned all of you, as I have warned myself and my colleagues, that there are other aspects and sectors of our economy that ought to be looked at by all of us and the government with regard to cost effectives. We should not simply make cuts in perhaps the biggest business in America.

I agree with you. But you know that we will have to look at the issue of limitless. . . .

MRS. BRODY. No I don't buy that. I don't think we should ever have to think cost effective in dollar terms when it comes to preserving humanity. I think to go along with that is amoral.

DR. ELSTER: Perhaps Dr. Eisdorfer would like to address this subject. He will be taking the position of president of a medical center where he will be responsible for allocation of resources.

DR. EISDORFER: Yes, I wish I had Elaine making the appropriations. I think it is fairly clear that setting up an ideal is important because without ideals we don't know where to go. The notion that Elaine has put forward is one that I think we have to examine. Taking my new President-elect role seriously, I rejoined for the third time the American Public Health Association. Periodically, they may get me angry and I quit every so often, but I have rejoined again and again.

The first journal issue I got was the symposium on the cost of defense in relation to health care. I recommend it to you. It is about two-months old, and it is a meticulous analysis of what it costs to defend this country, and at what expense.

It is very clear now, where we have gone. It is also very clear that we do not have an unlimited set of resources, whether they are hospital beds or renal dialysis machines. The simple truth is that you have to make ends meet. All you can do is establish a couple of very important principles.

First, life is precious, no matter what the age of the patient. Second, I think we finally have gotten a very important medical advance. It was not put forward as an advance in endocrinology. The greatest advance of the last couple of decades is the recognition that physicians are not God, nor are we God's surrogates. We are people, who have very high degrees of technical training and sophistication. Some of us are lucky enough to know a little bit about how to talk and listen to other people. More and more, we are saying that an individual has to be responsible for and responsive to the needs for health and medical care.

David Baseline had a discussion about the early stages of renal dialysis. Here we have a great technical capability of keeping people alive, who we know would die within days or weeks. Who do you put on the machine? Who don't you, given that you have 1000 people and room for 20. The question is, in a sense, not so much who you put on the machine, but how do you make the decision? The decision making process which involves sharing limited resources, cannot be made in camera any more. It cannot be made quietly in a closet which a) reinforces the God-like posture of the person making the decisions, and the mystifying power of that person and b) it does not let the public know that resources are limited.

This thing has an effect that cuts both ways. The more we share responsibility and power, the more people will work with us to get resources. Conversely, in medical school we felt we were something special. This image has been reinforced for a long time. We now have to recognize that being special involves doing some special kinds of things. The toughest thing I know how to do is share power. I think that is the answer to the question. Sure, we need more resources, but we first must learn how to share how we go about making these very tough decisions.

DR. LIBOW: I have a question for Dr. Andres. The curing of diabetes, as you humorously alluded to, by exchanging the criteria and reducing the prevalence in 20% of cases to something like three or five percent is an intriguing concept. Do you think that what we are seeing is a realization by the health care establishment, the experts in diabetes, that we need to look at the Andres-generated age adjusted criteria? Or, do you think that some of this is that we are in a cost effective era which is a dangerous phase. Government pressures, physicians in authority and others are starting to redefine illness by reducing the number of patients so thereby reducing the cost to the government and therefore to society.

DR. ANDRES: The former not the latter. I am sure that the Diabetes Data group had no thought whatever about cost effectivess. It was just time to face some very stupid things going on and fix them.

I don't know why it happened in 1979 instead of 1929, but that is the way it went. We should be grateful that it happened at all. They did not have in mind that this would have a fantastic economic impact. If they had thought of cost effectiveness, they would have put it in their report.

DR. ELSTER: I would like to conclude by asking each panel member if there is something particular he or she would like to say at this time before we conclude the proceedings.

DR. ANDRES: I hate to bring up dying again, but Dr. Longcope, Chairman of the Department of Medicine at Hopkins in the 30s and 40s is reputed to have said "in our effort to delay dying, we have to be careful that we don't kill the living," which sums up a lot of things that were said earlier.

DR. ELSTER: Since there are no more comments, we thank you and will see you tomorrow for section II of our symposium.

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Pneumococcal Pneumonia and Pneumococcal Vaccine

Robert Austrian, M.D.

Abstract

Pneumococcus remains a major cause of community-acquired bacterial pneumonia, an illness associated with significant mortality when accompanied by bacteremia, even when treated with potent antipneumococcal drugs. Death of those at high risk thereof results usually from irreversible physiologic injury which occurs early in the course of infection before treatment is begun. In addition, pneumococcal strains resistant to one or more antimicrobial drugs are being isolated with gradually increasing frequency. Both situations provide a rationale for prophylaxis and have led to redevelopment of polyvalent pneumococcal vaccine. Its use is recommended for those over 55 years of age and for those with a variety of systemic illnesses which place them at increased risk of death from pneumococcal infection.

Of the ten leading causes of death in the United States today, pneumonia ranks fifth and is the only disease of infectious origin in this category. In recent years, it has been responsible for 55,000 to 70,000 fatalities annually.

Of the estimated cases of pneumonia of all causes occurring each year, the exact number caused by each of the several microbial pathogens which may infect the lungs is unknown, including that resulting from infection with the pneumococcus. Pneumococcal pneumonia is no longer a reportable illness, and antimicrobial therapy prior to obtaining sputum and blood for culture may make accurate diagnosis difficult or impossible. In the absence of precise epidemiologic information, therefore, extrapolations from fragmentary data provide the best available basis for making estimates of attack rates which are broadly indicative of the frequency of pneumococcal pneumonia. From studies in hospitals where the disease has been closely monitored, it would appear to remain the most common form of community acquired bacterial pneumonia, the incidence of which has probably not changed significantly since the introduction of antibiotics.

The pneumococcus was isolated first in September, 1880, by George Miller Sternberg, later Surgeon General of the United States and founder of the Army Medical School, who recovered it from the blood of a rabbit inoculated with his saliva. Three months later, Pasteur isolated a similar organism from a rabbit inoculated with the saliva of a child who had just died of rabies. Both of those from whom the first two strains of pneumococci were recovered were carriers of the organism, and several years were to elapse before its role as a pathogen of man was clarified. Weichselbaum, in 1886, established the pneumococcus as the principal cause of human lobar pneumonia, a disease characterized at the turn of the century by Sir William Osler in the early editions of his famous textbook, *The Principles and Practice of Medicine*, as "Captain of the men of death." It was a greatly feared disease, attacking persons of all ages, and one accompanied by a mortality of 30% in the absence of treatment.

Recognition of different pneumococcal capsular types in Germany by Neufeld and Händel in 1910 and extension of these observations by investigators at the Rockefeller Institute and elsewhere permitted, for the first time, a rational approach to serotherapy. Shown at first to be beneficial in the management of infections caused by capsular type 1, treatment of pneumococcal pneumonia with type specific antiserum, produced first in horses and later in rabbits, was the mainstay of therapy for two decades.

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With the introduction of sulfapyridine in 1938, physicians had for the first time an agent for treating pneumococcal pneumonia effective irrespective of the infecting capsular type of causal organism. Less than a decade later, penicillin was introduced and proved even more potent. It is instructive to read the first report of its use, published in 1945, describing a dosage regimen of 10,000 units four times a day to manage either bacteremic or nonbacteremic pneumococcal pneumonia. Following the advent of penicillin, serum therapy for pneumococcal pneumonia, which required isolation and identification of the capsular type of the infecting pneumococcus, was abandoned; and typing serum ceased to be available soon thereafter. This latter event resulted in declining recognition of the pneumococcus in diagnostic laboratories. Coupled with the marked improvement in prognosis resulting from antimicrobial therapy, these changes led many to believe that the incidence of pneumococcal infection had declined markedly and that what remained was not of grave concern.

The views just cited were shared to some extent by the staff of one of the New York City hospitals which I joined in 1952. To determine whether or not this impression was correct, a special laboratory was established to isolate and to type pneumococci, and the practice of obtaining blood and sputum for culture from all patients with a clinical diagnosis was made routine. It became rapidly apparent, as a result of these measures, that the incidence of pneumococcal pneumonia had been greatly underestimated, in fact, by more than 90 percent. Indeed, there was no evidence that the availability of antibiotics had reduced in any significant way the incidence of pneumococcal infection.

The study, initiated in the manner described, was continued for a decade at the end of which period the data collected were analyzed. Because the presence of a pneumococcus in a culture of sputum expectorated through the oropharynx does not establish with certainty its causal role in disease of the lungs, the analysis was focused chiefly on bacteremic pneumococcal pneumonia because the isolation of a pneumococcus from blood establishes it as an unequivocal cause of infection.

Of the 529 bacteremic pneumococcal infections seen between 1952 and 1962, 455 were pneumococcal pneumonias uncomplicated by an extrapulmonary focus of infection and accompanied by a mortality of 20%. If the illness was complicated by pleural empyema, arthritis or meningitis, the mortality was more than twice that of uncomplicated bacteremic pneumococcal pneumonia. Despite the availability of antibiotics, the mortality of bacteremic pneumococcal meningitis, irrespective of its pathogenesis was also high, exceeding 50% among those over the age of 40.

Of 454 patients with uncomplicated bacteremic pneumococcal pneumonia, 17 received no antipneumococcal therapy either because they arrived at the hospital moribund and succumbed before it could be administered or because they developed fever of cryptic origin and died before its cause was identified. In this small group, the mortality was 82%, similar to that in a large series of similar patients observed before effective drugs were available. Among the 437 patients treated with antipneumococcal drugs, 75 or 17% died, a not insignificant death rate.

Several factors influence the prognosis of bacteremic pneumococcal pneumonia, among them the capsular type of the infecting pneumococcus, the age of the patient and the presence or absence of underlying systemic illness.

Not all 83 pneumococcal types are equally invasive, and mortality from infection with different types varies. Uncomplicated bacteremic type 1 pneumococcal infection treated with penicillin had a mortality rate of 7%. In contrast, similar infection caused by pneumococcus type 3, which occurs more often in older persons, had a fatality rate of 48%. The percentages dying of those with bacteremic infection caused by other common pneumococcal types fell between those of types 1 and 3. Any infection with a mortality of nearly 50% treated with the best available antibiotic, such as bacteremic type 3 pneumococcal pneumonia, must be regarded as a serious clinical problem. Even in the absence of bacteremia, putative infection with this pneumococcal type in persons over 50 years of age treated with penicillin had a mortality of 25%.

Age is an important prognostic factor. In patients under the age of 50 years with bacteremic pneumococcal pneumonia treated with penicillin, 7% died. In those 50 years of age and older, this figure rose to 28%. Similar observations are to be found in a study of bacteremic pneumococcal pneumonia carried out in a hospital in Chicago in the late 1960's.

The presence or absence of underlying systemic illness at the time the patient is striken with bacteremic pneumococcal pneumonia also affects significantly the likelihood of recovery or death. Among those in good health at the onset of infection, the mortality was 6%. In contrast, among

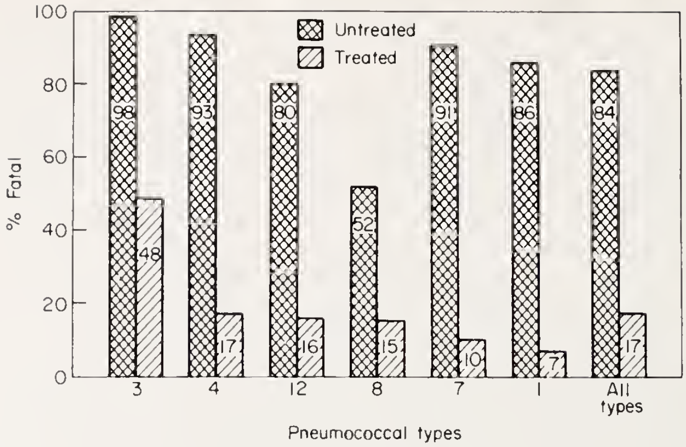

FIG. 1. Fatality in untreated and penicillin treated pneumococcal bacteremia (Austrian, 1964). Numbers within bars in this and subsequent figures indicate the percentage of fatal cases. Unless otherwise indicated, untreated and serum treated cases from Tilghman and Finland (1937). Printed with permission from Annals of Internal Medicine (Ref. #1).

those with a variety of chronic illnesses including cardiac, pulmonary, hepatic and renal disease, diabetes and other endocrinopathies, hematologic disorders and malignancies prior to developing bacteremic pneumococcal pneumonia, the mortality was 27%, exceeding one in four of those treated with penicillin.

If these three prognostic factors, that is, the capsular type of the infecting pneumococcus, the age of the patient and the presence or absence of underlying systemic illness, are combined, one can define a population at high risk of death from bacteremic pneumococcal pneumonia treated with antimicrobial drugs to which pneumococci are sensitive. It includes those infected with one of the six to twelve most invasive pneumococcal types who are 50 years of age and older and/or have one of the chronic illnesses cited earlier. It is a group which resembles strikingly in its characteristics that at high risk of death from viral influenza.

An additional finding of interest emerges from study of the survival curves of patients with bacteremic pneumococcal pneumonia treated with symptomatic care alone, with type specific antipneumococcal serum or with penicillin. In the five days following the onset of illness, the three curves are essentially superimposable. The finding indicates that, for those destined to die shortly after being stricken, therapy now available can do little to improve the outlook for their recovery. These individuals are ones who sustain very early in the course of illness physiologic injury, the nature of which is not understood and which cannot be corrected by antimicrobial drugs and empiric

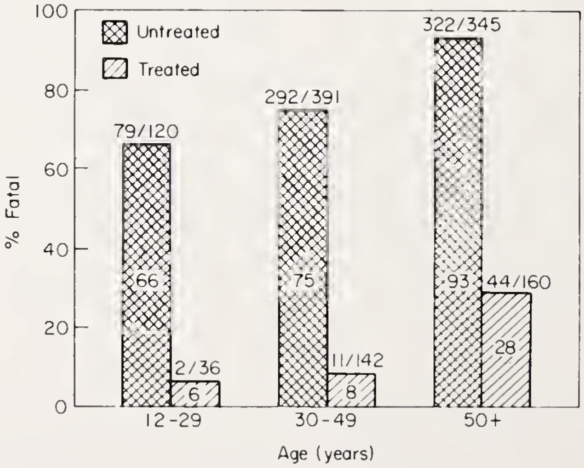

FIG. 2. Age-adjusted fatality in untreated and penicillin treated pneumococcal bacteremia (Austrian, 1964). Denominator of fraction above bar indicates total number of cases, numerator, number of fatal cases. Data for untreated cases include those of Bullowa (1937) and of Tilghman and Finland (1937). Printed with permission from Annals of Internal Medicine (Ref. #1).

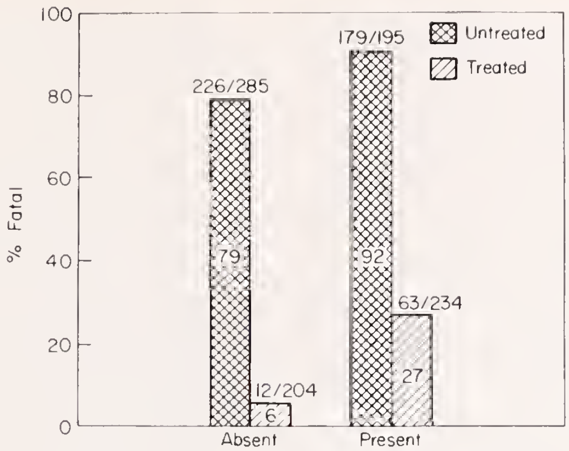

FIG. 3. Effect of complicating illness on fatality in untreated and treated pneumococcal bacteremia (Austrian, 1964), including all patients treated with antibiotics. Printed with permission from the Annals of Internal Medicine (Ref. #1).

measures alone. Approximately 60% of all deaths from this infection occur in this five-day period. If the mortality of bacteremic pneumococcal pneumonia is to be reduced now with knowledge currently extant, it will be necessary to prevent those individuals at high risk from death from becoming infected. An additional reason for considering a prophylactic approach to pneumococcal infection is the slowly increasing recognition of drug resistant pneumococcal isolates and the occurence, in several areas, of strains sensitive only to vancomycin among the drugs used to treat it.

Attempts to prevent pneumococcal pneumonia by vaccination began seventy years ago when Sir Almroth Wright, who developed typhoid vaccine, went to South Africa seeking to control the ravages of this disease among native gold miners. At that time, the mortality among miners was so high that it threatened the continued existence of the gold mining industry. Wright used a vaccine of unknown composition which was administered to approximately 50,000 men. Although he was convinced of the vaccine's efficacy when the trial was completed, analysis of the data raised questions about this conclusion. Wright's protégé, F. Spencer Lister, an English emigré to South Africa, contributed significantly to a better understanding of the problem. He identified the type specific nature of immunity among men recovering from pneumococcal pneumonia, established the proper dose of killed pneumococci required to immunize humans and could have demonstrated conclusively the efficacy of pneumococcal vaccine had his trials of it been structured differently.

Discovery of the immunogenicity of pneumococcal capsular polysaccharides in mice in 1927 and in man in 1930 led to the replacement of whole bacterial vaccines with these chemically definable antigens in subsequent studies. In the 1940's, MacLeod, Hodges, Heidelberger and Bernhard demonstrated conclusively, in an elegantly planned and executed trial of a tetravalent vaccine of pneumococcal capsular polysaccharides, that these antigens conferred a high degree of protection against type specific infection. As a result of this and related studies, two hexavalent pneumococcal vaccines were marketed in this country after World War II, but they were little used because of the optimistic assessment of antimicrobial therapy prevailing at the time and were soon withdrawn by their manufacturer.

To develop the vaccine now available, a number of requirements had to be met. To determine the most prevalent and invasive of the 83 pneumococcal capsular types, more than 3,000 isolates from blood isolated by colleagues in municipal hospitals across the country over a ten-year period were typed. Half the infections were caused by serotypes 1,3,4,7,8 and 14, another quarter by serotypes or -groups 6,9,12,18,19 and 23 and another eighth by six additional serotypes or -groups. Fourteen strains representing the capsular serotypes or -groups accounting for 80% or more of bacteremic pneumococcal infections were chosen for inclusion in the vaccine. The polysaccharides of these 14 strains were purified and studied in volunteers. Sequential injection of several polysaccharides into volunteers showed the immunologic response to each to be independent of those to the other antigens. Polyvalent pneumococcal vaccine is, in fact, 14 independent vaccines combined in a single formulation, a fact to be borne in mind in assessing its efficacy. From dose-response studies, it was determined that a suitable dose of each polysaccharide for immunizing adults was 50 μg.

The safety of the vaccine was demonstrated by its administration to gradually increasing numbers of volunteers without significant untoward effect. Among 6,500 persons over the age of 45 who were given the vaccine, 60% had no reaction whatever. Forty percent had some pain or discomfort and 35% had some redness and induration at the site of injection, and 3% had moderate elevations of temperature lasting up to 36 hours in contrast to similar reactions seen with a frequency of 1% in the randomized control population. The more severe reactions were quite similar to those observed commonly after the administration of typhoid vaccine.

Persistence of antibodies following recovery from pneumococcal infection appears to result in life long immunity to the infecting pneumococcal type. The decay of levels of antibodies following immunization with pneumoccal vaccine follows roughly the same time course as that after recovery from infection, so there is a presumption that immunity resulting from vaccination will be long-lived. For that reason and because there appears to be a direct correlation between the aggregate level of antibodies to the antigens in the vaccine prior to its injection and the severity of reactions to it, reimmunization with pneumococcal vaccine at intervals of less than five years is not advised.

To demonstrate the efficacy of the vaccine, controlled trials were conducted in the United States and also in Africa because of the persistance of high attack rates of pneumococcal infection in the latter area. In the African trials involving young adult gold mining novices, 4,000 men received pneumococcal vaccine, 4,000 men were given meningococcal vaccine and 4,000 a saline placebo. There was a 78.5% reduction in putative pneumonia and/or bacteremia associated with the pneumococcal types, the polysaccharides of which were contained in the vaccine. The p value for the difference between pneumococcal vaccinees and the two control cohorts was less than 0.0001. Because of the complexity of pneumococcal vaccine, it was of importance to demonstrate the efficacy of at least some of its individual components. Analysis revealed marked reductions in the occurrence of disease caused by types 1,2,8,12 and 25 in pneumococcal vaccinees when contrasted with controls, the p value for the observed differences being, in each instance, less than 0.01.

The occurrence of ten bacteremic infections with types in the vaccine in pneumococcal vaccinees was a cause of some concern. On further analysis, eight of ten proved to have been caused by pneumococcus type 1. Reassay of the vaccine employed revealed that it contained only 9 μg of type 1 capsular polysaccharide per dose instead of the purported 50 μg. Although the dose employed affected a 72% reduction of type 1 pneumococcal infection in the pneumococcal vaccinees, it is evident that 9 μg of capsular polysaccharide is a suboptimal dose in the adult human.

Because pneumonia is a disease of diverse origins, the possibility always exists that disease caused by some pathogens and eliminated by vaccination will be replaced by illness caused by other pathogens. In this African population, in which pneumonia caused by pneumococcal types in the vaccine predominated, there was a 50% reduction in radiologically confirmed pneumonia over a two-year-period, irrespective of cause, in the pneumococcal vaccinees as contrasted with the

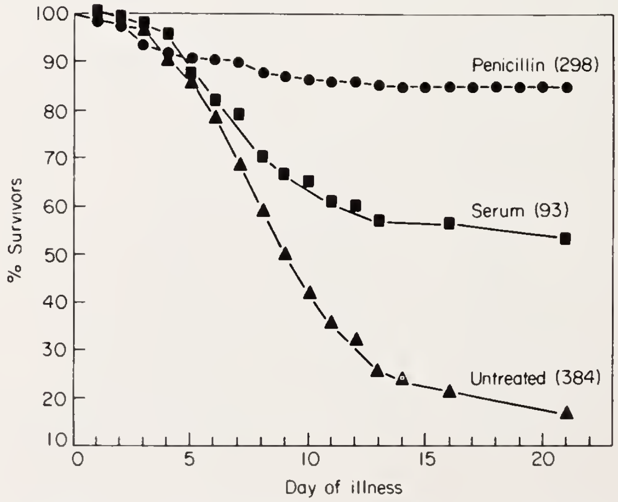

FIG. 4. Effect of therapy on per cent survival in pneumococcal bacteremia (Austrian, 1964). Numbers in parentheses indicate size of each group of patients. Serum treated patients include only pneumococcal types 1 and 2. Printed with permission from the Annals of Internal Medicine (Ref. #1).

control populations, with the difference having a p value of less than 0.0001. Whether or not this reduction would have been maintained indefinitely cannot be stated.

The two trials conducted in the United States proved less definitive for several reasons, although their results are in accord with those of the other trials of pneumococcal vaccine. One was conducted in a hospital for chronic illness in North Carolina, the other in a prepaid health plan in California and involved nonhospitalized subscribers over the age of 44. In each trial, the attack rate of pneumococcal infection was low at the time it was conducted, and little bacteremic infection was observed. It was necessary to rely, therefore, on serologic confirmation of the diagnosis of type specific pneumococcal infection both in control subjects and in vaccinees. Interpretation of immunologic data from immunized subjects is difficult because reexposure of man to bacterial polysaccharide antigens is followed frequently by little or no change in the level of antibodies antedating such reexposure. All that can be said is that, on the basis of serologic data, there was an 80% reduction in immunologically confirmed pneumococcal infection associated with types in the vaccine in the vaccinees in each trial and that the results were concordant with those of all other trials of pneumococcal vaccines. On the basis of these and of other data, the vaccine was licensed late in 1977 and made available for use in 1978.

Pneumococcal vaccine may be recommended to persons over 6 years of age with any of the chronic systemic illnesses cited earlier, including those with congestive heart failure, chronic pulmonary, renal or hepatic disease, diabetes, hematologic disorders and a variety of malignancies. Patients with anatomic or functional asplenia, including those with sickle cell disease, are at significantly increased risk of fulminant pneumococcal sepsis and may succumb within 48 hours of the onset of illness with a clinical picture resembling that of the Waterhouse-Friderichsen syndrome seen in meningococcemia. It should be remembered also that infection with pneumococcal types not included in the vaccine may occur in these individuals; and, depending upon circumstances, concomitant chemoprophylaxis may require consideration in children.

With regard to the healthy elderly, more needs to be learned from continued study of the vaccine. There is good evidence that the attack rate of pneumococcal bacteremia rises in later life and exceeds significantly that of tetanus, a disease for which universal prophylaxis is recommended. Because of the persistance of antibodies following immunization and because many of the elderly will develop illnesses placing them at higher than average risk of death from bacteremic pneumococcal infection, it seems advisable to offer pneumococcal vaccine to persons attaining the age of 55 years.

Patients with a variety of immunologic disorders are unlikely to benefit significantly from pneumococcal vaccine. Among them are persons with multiple myeloma, lymphatic leukemia, hypogammaglobulinemia or ones who have been treated intensively with immunosuppressive therapy. If such individuals elect to be vaccinated, they should be advised of the possible failure of the vaccine. Patients with Hodgkin's disease respond immunologically to pneumococcal vaccine if given it two weeks or longer in advance of treatment of their disease, but levels of antibody may decline after therapy is initiated.

The immune system of man is not fully developed at birth, and adult levels of some classes of immunoglobulins are not achieved until the age of 6 or more years. As a result of this developmental phenomenon, children may fail to respond immunologically to some polysaccharide antigens of bacteria and to be protected by vaccines composed of them in the first years of life. Studies are in progress seeking ways to improve the immunogenicity of these antigens in the very young.

In conclusion, pneumococcal vaccine represents an addendum to the armamentarium for the control of respiratory infections of man. It is safe, antibodies to its components persist for long periods, and it should confer significant benefit on those at increased risk of severe or fatal pneumococcal infection.

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QUESTIONS AND ANSWERS

Question: Is it safe to give pneumococcal vaccine at the same time you give influenza vaccine?

Dr. Austrian: Yes, it is safe, although the likelihood of some reaction will be moderately increased over that which follows the administration of either vaccine alone. Studies have been done in which the two vaccines were given simultaneously without the occurrence of significant untoward effects. The two vaccines should be administered from separate syringes and injected at separate sites if given at the same time. Antibody responsiveness to the antigens in both vaccines given under these conditions is satisfactory.

Question: Why is revaccination recommended every five years?

Dr. Austrian: The package insert does not recommend revaccination at all. It states that the patient should not be reimmunized at intervals of *less than five years*. Persistance of antibodies and the association of higher levels of antibodies before immunization with reactions to the vaccine make its readministration at short intervals undesirable and probably unnecessary.

Question: How soon is resistance acquired after vaccination?

Dr. Austrian: It takes about two weeks for most individuals to develop protective levels of antibodies to the antigens in the vaccine. In trials conducted in a population with a high attack rate of infection caused by pneumococcal types in the vaccine, evidence of the protective effect of the vaccine was detectable after one week, but did not reach its maximum for another week.

Question: Why doesn't Medicare pay for pneumococcal vaccine?

Dr. Austrian: As of the moment, there is a legislative provision for Medicare to pay for the costs of pneumococcal vaccine for persons 65 years of age and older.

Question: What percentage of the pneumonias in chronic care institutions and nursing homes is pneumococcal?

Dr. Austrian: The question is a difficult one to answer because of the paucity of precise information. In the one institution for which relatively complete data are available, pneumonias caused by pneumococcal types in the vaccine accounted for about 11% of radiologically confirmed illness of this kind. The proportion of pneumonias caused by pneumococci will doubtless be influenced by a variety of factors, including the ages and general state of health of the population at risk, the rate of turnover of members of the population, etc. What is found at one institution at a given time and place may not be applicable to another institution with other demographic features.

Question: Will the long term use of the available vaccine increase the incidence of pneumococcal pneumonia caused by types that are not in it?

Dr. Austrian: The possibility raised is one that cannot be excluded, although there is no concrete evidence at the moment to support such an hypothesis. Replacement of disease eliminated by vaccination in the African trials by illness caused by other pneumococcal types or by nonpneumococcal respiratory pathogens was not observed over a two-year period. Many pneumococcal types not in the vaccine appear to be relatively less invasive than those which are in it.

Question: On the basis of age or of illness, are there any patients who should not be given the vaccine?

Dr. Austrian: The vaccine is not licensed for administration to children under 2 years of age because of its limited immunogenicity and lack of proved efficacy in this age group. It is recommended also that the vaccine not be given to pregnant women or to individuals with active infection.

Question: May the vaccine be given to patients being treated with a steroid?

Dr. Austrian: Low doses of congeners of adrenocorticosteroids do not diminish immunologic responsiveness to pneumococcal vaccine although other forms of immunosuppresive therapy may do so if they result in destruction of the appropriate lymphocyte population.

Question: Can the vaccine cause an infection?

Dr. Austrian: The vaccine is composed solely of chemically definable bacterial polysaccharides. It contains no viable or intact microorganisms and **cannot** cause infection.

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The Current Status of Cataract and Intraocular Lens Implant Surgery

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Cataract extraction is not only the most frequently performed intraocular operation, it is the most frequently performed operation in the geriatric patient. It is estimated that 450,000 cataract extractions are performed annually in the United States. An intraocular lens implant is used in approximately 150,000 of these. The past 30 years have witnessed a much more liberal approach to the indications for cataract surgery. This tendency has been especially apparent in the United States, where the number of cataract operations performed per capita population considerably exceeds that in any other country in the Western World. This development has resulted in some criticism from those who maintain that this more liberal interpretation is not medically, socially, and economically justified. The controversy has placed ophthalmology in the "eye" of a surgical storm (1).

A technologic explosion has arisen both in the techniques of cataract extraction and in the optical correction of aphakia. This whirl of technologic advances has had an intoxicating effect on American ophthalmology (2). A dilemma faces every responsible ophthalmologist. The lay press, on the one hand, has heightened public expectation by making the most heroic surgical procedures appear conventional. Consumer groups, on the other hand, label new advances as bordering on human experimentation. The American ophthalmologist appears to have reacted by yielding to public pressure and the challenge of modern technology. How else can one explain the 450,000 cataract extractions performed annually in the United States?

Public pressure is not without some justification. The geriatric patient lives longer, enjoys better health, is increasingly active, demands better vision, and drives an automobile through old age. Public pressure has kept pace with modern advances in cataract surgery. Thirty years ago, it would have been unthinkable to remove a cataract because of the disturbance of glare in direct sunlight or the visual distortions of oncoming headlights of an automobile during night driving. What technical advances then have encouraged patients with cataracts to seek early solutions to their visual problems? These are mainly to be found in refinements in the technique of cataract extraction and in the optical correction of aphakia.

Technique of Cataract Extraction

The extracapsular method of cataract extraction was in vogue about 40 years ago. In this procedure, the anterior capsule and the lens were removed while the posterior capsule of the lens was left in situ. It was necessary to wait until the cataract was nearly mature and the eye nearly blind because nonopaque parts of the lens were difficult to remove. This delay placed many patients in a severely visually handicapped state for a long time before the operation could be performed. Therefore, it is easy to explain the ethusiasm that met the introduction of the intracapsular method of cataract extraction, which permitted total removal of the lens. This procedure has become considerably safer over the past four decades as a result of preoperative methods of lowering the intraocular pressure (3), the discovery of alpha chymotrypsin to lyse the suspensory ligament of the lens (zonular fibers) (4), the technique of cryoextraction (5), improved methods of making the surgical incision (3), and improved suture materials and needles to ensure secure closure of the incision (6). Early postoperative ambulation of the patient became possible resulting in a sharp decline in the incidence of postoperative behavioral disturbances, embolic phenomena, and prostatic obstruction.

The intracapsular method remained unchallenged until 1967, when the phacoemulsification procedure was introduced (7). This operation permits emulsification of the lens nucleus with an ultrasonic vibrating needle, and irrigation and aspiration of the remaining corical lens material. A substantial advantage of this ingenious method is that the entire procedure, when uncomplicated, can be performed through a 3 mm incision, allowing immediate ambulation and return to full activity with minimal delay. An offshoot of the phacoemulsification method is the modern planned extracapsular cataract extraction in which the anterior lens capsule is opened and the nucleus of the lens is expressed. This requires a larger incision, yet significantly smaller than that required for an intracapsular cataract extraction. The enormous advances in the extracapsular method over that practiced 40 years ago are the availability of the surgical microscope and machinery which can safely remove all residual nonopaque lens material.

The intracapsular-extracapsular controversy is currently one of the most hotly debated subjects at ophthalmologic meetings throughout the world. Both the phacoemulsification and the extracapsular method leave the posterior capsule of the lens in position within the eye. Proponents of these techniques feel that this provides stability within the eye which results in a lowered incidence of postoperative cystoid macular edema and retinal detachment. Although still debated, there is mounting evidence that this premise is valid. My own studies show conclusively that postoperative cystoid macular edema occurs approximately five times more frequently after an intracapsular than an extracapsular cataract extraction.

These technologic advances have spawned a new era of super surgeons. The demands of modern extracapsular surgery including phacoemulsification, especially when combined with intraocular lens implantation, place this surgery beyond the technical expertise of the average or below average surgeon. This explains why 85% to 90% of surgeons still use the intracapsular method. Most of the expert large volume surgeons have turned to the extracapsular technique. Until a surgeon updates his surgical skills, it is definitely in the best interests of his patients for him to perform the kind of surgery with which he is most comfortable. Residency programs throughout the nation are providing training in these new methods. There are also numerous training programs for the more experienced surgeon. I predict that within the next decade the preferred method of cataract extraction will be the planned extracapsular cataract extraction or phacoemulsification, both of which leave the posterior capsule of the lens within the eye.

Optical Correction of Aphakia

A successfully performed cataract extraction is only the first step in the visual rehabilitation of the patient. The removal of the patient's lens creates such formidable optical obstacles that it has been stated that the "first complication of cataract surgery is aphakia" (8). The traditional method of correcting the problem by using a cataract spectacle creates many difficulties. Objects are magnified about 30%, and peripheral vision is considerably reduced. Objects in the environment which are invisible suddenly appear as the patient's eye turns (Jack-in-the-box phenomenon). These visual impairments place the patient in a severe state of spatial disorientation, and the performance of simple tasks such as placing a key in a lock, walking up and down a flight of stairs and pouring coffee into a cup may become very difficult, though many patients finally adjust to this situation.

Some of these problems have been considerably eased by the use of contact lenses. Objects are only magnified by 5% to 10%. Contact lenses provide nearly complete visual rehabilitation in patients who have undergone cataract extractions in one or both eyes, provided they can master the insertion and removal of the lenses and can wear them comfortably. Most elderly patients (over 70 years) and most with infirmities such as rheumatoid arthritis, Parkinsonism, hemiplegia, and mental retardation cannot handle contact lenses. It is hoped that the extended wear contact lens will remove some of these obstacles. Unfortunately, they are not highly successful in patients with dry eyes and those with poor eyelid hygiene. Yet they have achieved significant success in a high number of aphakic patients. These lenses are easy to fit and kept on the patient's eye without removal for up to six months at a time. Therefore, they represent a real alternative for the intraocular lens. Many ophthalmologists consider contact lenses (hard, soft, or extended wear) as the safest method of correcting aphakia in patients under 65 years of age.

The most exciting new development of the last 15 years has been the use of intraocular implant lenses. Approximately 500,000 of these lenses have been used in the United States. This process involves the placement of a plastic prosthetic lens inside the eye to replace the cataractous lens. The intraocular implant lens produces only 1% to 3% magnification. None of the problems of spatial disorientation or abnormal peripheral vision associated with cataract spectacles occur. The advantages of these lenses in the elderly and in others unlikely to succeed with contact lenses are enormous.

Although the efficacy of the intraocular implant lens is now generally accepted, some question about its safety remains. The surgical procedure is technically more difficult than a routine cataract extraction. The rate of surgical complications is therefore greater, although only slightly greater, according to present knowledge (9). The degree varies with the skill of the surgeon. The surgeon must also depend on quality manufacture of the lens implant.

Intraocular lenses had a stormy history starting with the first modern lens implant procedure performed by Ridley of England in 1949. The results were highly disappointing until 1958 when safer implants were introduced. There has been a striking increase in the safety of these lenses as a result of newer techniques of implantation and increased quality of their manufacture. Lens implants fall into three categories according to their placement inside the eye. Anterior chamber lenses are supported by the angle of the anterior chamber. These can be used with an intracapsular or extracapsular cataract extraction. Iris supported lenses and iris and capsule supported lenses are showing a slight decrease in popularity. The former may be used with intracapsular or extracapsular surgery whereas the latter require the presence of the posterior lens capsule for fixation and therefore can only be used with an extracapsular extraction. There has been a recent increase in enthusiasm for posterior chamber lenses which are placed behind the iris in virtually the same position occupied by the human lens. The drawback here is that they can only be used with an extracapsular cataract extraction. The cataract surgeon now has at his disposal numerous types of intraocular lenses which he can adapt to his preferred method of cataract extraction.

The Food and Drug Administration has been monitoring the progress of lens implant surgery since the passage of Devices Legislation in 1976. Approval will be granted to manufacturers after evaluation of their products in the hands of investigative surgeons. This is the largest evaluation of a surgical procedure in medical history. An interim report was presented in 1979 involving more than 177,000 cases. This figure will increase enormously during the next two years. The interim report was generally favorable to the safety of intraocular lenses in the short term (10). This confirms other clinical reports (11, 12).

Many ophthalmologists now consider intraocular lens implantation to be the procedure of choice for elderly patients and infirm patients who are incapable of managing a contact lens. (13) In a patient with bilateral cataracts, a unilateral implantation may be adequate for the patient's needs. This single implantation is of particular advantage in an elderly patient, in whom one operation may be sufficient. Such a patient is more rapidly and completely rehabilitated than a patient who is bilaterally aphakic and wearing spectacles.

Decision to Operate

The issue of increasing cataract surgery in the United States is highly controversial. Investigations of unnecessary operations are attractive to the mass media and often result in erroneous interpretation of the physicians' motives. It is difficult to establish a set of guidelines for the indications for cataract surgery. Patient need and surgeon skill vary enormously. However, most responsible ophthalmologists have followed a set of guidelines based entirely on patient need and a personal assessment of their own surgical expertise.

Faced with a patient whose cataracts have lessened his vision, the surgeon must meet this challenge with mature judgment. The only pertinent question is whether the operation will benefit the patient. The surgeon's ability to achieve a successful anatomic result is of lesser importance. It is impractical to assign a particular level of visual acuity as the appropriate one for cataract surgery. It may not be well understood that a patient with 20/30 to 20/40 visual acuity may be far worse off than one with 20/100. If the lens opacity is located in the direct visual axis, for example as in a posterior subcapsular cataract, the patient may read the smaller lines of the Snellen vision chart in a darkened room since his pupil is slightly dilated in darkness and therefore the cataract does not occlude the entire pupil. However, the pupil is smaller when the patient is out in daylight. The lens opacity may then effectively block the entire pupillary aperture. The patient may also be unable to read since the pupil constricts during near vision. On the other hand, a nuclear cataract may reduce distance vision to a relatively low level, and yet these patients can often read a newspaper. Therefore, cataract removal can usually be delayed in these patients, particularly if they are elderly.

It may not be fully appreciated how disabled a person can be after a perfectly executed uniocular cataract operation. There are countless patients who have postoperative visual acuity of 20/20 in one eye after cataract operation but who find it impossible to use the eye because the opposite eye, not operated on, still has useful vision. A cataract spectacle cannot be worn unilaterally because there is a 30% difference in retinal image size between the unoperated eye and the optically corrected aphakic eye. It is common for patients to prefer to perform most manual and physical activities with the help of the eye not operated on even though it may have 20/60 to 20/80 vision because of an incipient cataract. This situation frequently causes the surgeon to recommend cataract extraction in the second eye to achieve binocularity. This may improve the situation but the patient may be little better off after two cataract operations than he was before the first operation. He now must wear aphakic spectacles with their optical disadvantages. Many such patients are sorely disillusioned after a "perfect cataract operation" has made them functionally more disabled. This problem was accurately described by a famous ophthalmologist after cataract surgery on both of his eyes (14).

The situation is different if the patient can manage a contact lens after surgery. The surgeon is then justified in removing the cataract from the poorer eye. Younger patients, who have greater need for stereoscopic vision, and those with special occupational needs are usually overjoyed with the result. Unfortunately, contact lens wear is not absolutely predictable. The patient may be unsuccessful with a contact lens, thus confronting the patient and surgeon with a serious dilemma. A secondary lens implant could be attempted but these are still considered more hazardous than a primary lens implantation (at the time of cataract extraction). An extended wear contact lens may be successful but many prove to be less successful in patients who cannot wear other types of contact lenses. If the patient is elderly and not likely to succeed with a contact lens, and if the surgeon is not well trained in lens implant surgery, it is probably better not to perform the cataract surgery at all.

Intraocular implant lens surgery most frequently meets the needs of the elderly patient. As stated above, there is a greater risk of complications with this type of surgery than with a routine cataract extraction. In the hands of a skilled, experienced surgeon, the risk is only slightly greater but it can be much greater during the early experience of the surgeon or with those less surgically talented. The surgeon, therefore, is faced with a personal assessment of his own capabilities. It is impractical to have this decision made for him. Another moral judgment faces the surgeon: even if he can achieve a successful surgical result in a very high percentage of his cases, is he justified in performing this procedure in relatively young people? Most responsible ophthalmologists do not perform lens implant surgery in these patients since there are as yet no well documented clinical studies spanning more than 20 years of follow-up observation with intraocular lenses. Therefore, if the patient is young (under 55 years of age), the serious question of the long-term tolerance of the lens implant remains. Moreover, younger patients are usually able to manage contact lenses successfully.

Although a technologic explosion has occurred in the techniques of cataract extraction and in the optical correction of aphakia, the patient benefits most when the surgeon adopts a modern attitude towards his patient based on old-fashioned values.

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Psychiatric Aspects of the Cardiac Patient

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The heart, probably more than any other organ in the body, has great symbolic and deep psychologic impact on psychic equilibrium. We say that a person has become "broken-hearted," "heart-sick," or "heavy-hearted" and may respond to a "heart-to-heart" talk following a rejection or a loss. The symbolic importance of the heart may be intensified in the elderly especially since real losses are inevitable and are superimposed on a disordered cardiovascular system. Existing cardiac disease may, be exacerbated by the mounting tension, anxiety, and frustration associated with loss or rejection.

Congestive failure is a useful model to investigate the effects of emotions on the heart. Patients with various forms of heart disease and limited cardiac reserve go into congestive failure as the result of either an increase in demand for cardiac work beyond the capacity of the myocardium or a decrease in the myocardial capacity below the basal work demand. Emotional stress has been implicated in congestive failure in most cardiology texts, but the data are often anecdotal.

Chambers and Reiser (1) have demonstrated that emotional stress is capable of increasing the demand for myocardial work, thus precipitating congestive heart failure in persons with a limited reserve. They studied 25 consecutive patients admitted for the treatment of congestive heart failure. Each patient, who primarily had hypertensive or arteriosclerotic heart disease, was interviewed daily for three days by an internist whose role was to "reach an understanding of the specific emotional meaning to the individual of his life situation at the time cardiac decompensation had developed," and to isolate from the multiple noxious factors that one "which appeared to be responsible for finally destroying the balance between cardiac reserve and demand for work." Precipitating factors were identified in 23 patients.

In 19 (76%), emotional tension was the factor immediately responsible for increasing the work load beyond the cardiac capacity. These tensions developed from recent life situations provoking feelings of rejection, insecurity, frustration, and rage. An example was a 72-year-old independent woman with long standing hypertensive arteriosclerotic heart disease and congestive heart failure who was obliged to live with a relative because of failing vision. One year later, she developed congestive heart failure after a social worker notified her that her relative was no longer able to sustain the living arrangements, and that she was being transferred to the County Home. In another case, an 83-year-old woman with arteriosclerotic heart disease, atrial fibrillation, and congestive heart failure of seven years' duration had a recurrence of heart failure six hours after the death of her husband.

This study has helped promote recognition of elderly cardiacs as a psychologically unique group of patients who may develop congestive failure when confronted with stress. These patients are immersed in a series of psychosocial life stresses which ultimately lead to feelings of insecurity, frustration, and rage. Moreover, these events occur at times when physical strength, attractiveness, and stamina have diminished. It becomes difficult to establish new interpersonal relationships or to develop new activities to compensate for these losses. Comprehensive management, therefore, must not only address the issues of structural heart disease but also the noxious life events which led to the emotional stress and those coping mechanisms available to the patient which will help him or her adapt to the losses.

The nature of certain presenting symptoms may also contribute to the psychologic problems experienced by the geriatric cardiac patient. If is often difficult to determine whether presenting symptoms such as easy fatigability, palpitations, light-headedness, and syncope are primarily somatic or psychiatric in origin. The initial enthusiasm of the physician performing a medical work-up wanes as negative results return. The ambiguity of the etiology of the chief complaint symptoms may lead to increasing anxiety both in the physician and in the patient. The patient and physician may believe that a negative work-up proves that the symptoms are, in fact, "in his or her head." Since these symptoms may be considered psychiatric in origin, there is an increased likelihood that psychotropic medications will be prescribed (2). The original problem, that is, lightheadness, is not compounded by psychotropic drug side effects which produce additional discomforts that the patient must cope with.

An example of this sequence of events is Mrs. M., a 76-year-old Italian woman who presented with lightheadness and minimal pretibial edema. She had been treated in the past for mild hypertension with Propranolol. A complete medical work-up revealed occasional PVC's on electrocardiogram and a suggestion of pretibial edema. She was placed on Digoxin (0.25mg/day) and Persantine. On her follow-up visit, she complained of lightheadness, palpitations, and a flushing sensation which started in her toes and traveled to her head, frightening her sufficiently to require a minor tranquilizer. On a return visit, her physician discovered that the lightheadedness began approximately two months after the death of her husband; therefore, a tricyclic antidepressant Imipramine Hydrochloride (25mg t.i.d.) was added to the drug regimen. Three days later the patient had an episode of syncope in the grocery store and subsequently developed a fear of leaving her home, concerned that she would faint without anyone around to help her. A psychiatric consultation was obtained for her presumed agoraphobia. A family consultation was arranged with the patient and all of her children. It evolved that the patient had experienced lightheadedness for many years but had learned to cope with the discomfort. Following the death of her husband she felt alone and needy but was afraid to ask any of her five children to visit on some regular basis. Instead, she would call her children and during the conversation mention that she was feeling lightheaded. The children responded to these frequent complaints by sending her to their physician, with the expectation that he would handle all her problems. After a diagnostic session, a treatment plan was developed with the family and treating physician to discontinue all medication, and have the children and grandchildren rotate visits to her home and take her out shopping. On follow-up, the patient's symptoms had cleared except for an occasional episode of tolerable lightheadedness. She was able to shop at the supermarket without difficulty if a relative accompanied her. Talking about a symptom may be a plea for help or for relatedness rather than evidence of psychopathology akin to depression or hypochondriasis. These problems fall into the grey area between medicine and psychiatry and can be more difficult to resolve if clear-cut signs and symptoms of cardiac disease are focused upon either as a plea for help, nurturance or relatedness.

Another obstacle to dealing effectively and comprehensively with the elderly cardiac patient is the physician's resistance to a long-term involvement with these patients and his unwillingness to explore the emotional aspects of presenting symptoms. This problem has been attributed to "gerontophobia," (3) which refers to the physician's aloofness to elderly patients resulting from his or her own fear of aging. As in any phobia, physicians may avoid their own unresolved conflicts with the aging process by projecting them onto the elderly patient and then simply avoiding the patient. The phobia enables the physician to avoid internalizing the conflict, but it also diminishes his capacity to work with the elderly. Butler has used the term "ageism" (4) to describe a therapeutic nihilism in the treatment of the "inevitable consequences of so-called aging." It is common that elderly patients with vague symptoms such as lightheadedness are (sometimes) called "crocks," giving rise to the "senile write-off." The patient's ailments are interpreted as trivial and are dismissed with one more prescription or with patronizing advice.

Although gerontophobia and ageism are helpful in providing an overview of the problem, Harry Stack Sullivan's (5) concept of selective inattention offers greater insight into the reasons for the physician's difficulty in working with the elderly. This concept postulates a dissociation from the physician's awareness of the unpleasant emotional realities, that is, seriously ill aging patients, with a concomitant focusing or distraction of attention to less threatening areas of inquiry such as signs or symptoms of disease or laboratory tests. It is a simple technique used by the physician to reduce felt anxiety and thus to maintain feelings of security and self-respect. This mechanism prevents one from learning "despite remarkable experiences that befall us, simply by keeping attention on something else" (symptoms, signs, laboratory tests) and by controlling our awareness of the events that impinge upon us. With this handicap, an emotional experience with an elderly patient is not felt, and, therefore, not profited from. In fact, we never notice the extent to which it has occurred. Selective inattention is not a serious problem when the irrelevant is disregarded. But when significant details such as the emotional meaning of symptoms are not attended to, the patient receives a "senile write-off." The longer selective inattention prevails, the more habitual and automatic the behavior becomes. It is only after we have recognized the extreme ease with which crucially important clinial details may be overlooked that we can properly confront paralyzing consequences of selective inattention. An encouraging aspect of this concept, however, is that persons selectively inattentive to an impinging event will be able to acknowledge the behavior if an observer or supervisor calls attention to it. The supervisor is encouraged to sit in during the initial interviews and point out instances of inattentiveness, intensifying the focus on those aspects of the interview that are selectively being avoided. Thus, if a patient describes symptoms of cardiac dysfunction and alludes to feelings of loneliness, directing the physician to focus on the patient's experience of aloneness will help bring out the patient's emotional state. After several supervised sessions, the physician may become aware that he or she consistently focuses attention away from the emotionally bleak, loss-ridden life of the elderly. This teaching model has been helpful in consultation-liaison psychiatry, especially when dealing with the chronically ill elderly patient.

In reviewing the development of psychiatric illness in the cardiac elderly, a physician should note that the onset of heart disease with subsequent hospitalization, diminished physical capabilities, and the possibility of death is viewed by the patient as a personal attack or narcissistic injury and may give rise to temporary feelings of free-floating anxiety, restless insomnia, grief, or reactive depression. The reactive depression represents the emotional side of the conscious awareness of the loss of an important aspect of one's physical/psychic functioning, and is associated with a decrease in self-esteem and self-worth. In spite of the narcissistic injury, these patients will respond to interactions with others, and the doctor may see a temporary lifting of the depressed mood and an underlying sense of humor. Therapy consists of a discussion of the symbolic and psychologic meaning of the heart disease, encouraging the patient to ventilate feelings of frustration or helplessness in the face of illness. Active cardiac rehabilitation directed toward what the patient can still do also contributes significantly to shortening the reactive depression.

Patients with chronic long-standing heart disease with recurrent periods of invalidism demonstrate other psychologic reactions. These patients are unable because of the high degree of invalidism to discharge unpleasant feelings through pleasurable activities and may respond to physical and emotional losses by withdrawing and becoming preoccupied with their own feelings and bodily functions. Feelings of hopelessness and frustration are released by struggling with relatives and hospital staff. This can be a powerful means of communicating and relating but the family may become increasingly resentful of these demands and either avoid the patient or shift the responsibility for relating or nurturing to the physician. The physician may respond to a similar situation with the use of polypharmacy of psychiatric referral. This form of hypochondriasis may be reactive in nature and may reflect disturbed communication with significant others (6).

Long-standing heart disease with invalidism may also lead to a state of demoralization which can often be distinguished from depressions requiring drug treatment. These patients appear despondent or apathetic and show a lack of interest in their environment or treatment. They appear anhedonic and have minimal spontaneity. Irritability may erupt into rage and destructiveness. Regression characterized by a childlike mode of relating may appear. Although defensive withdrawal is adaptive in acute illness when compliance to treatment is life-saving, its presence in chronic illness results in disturbed relationships characterized by egocentric behavior, lack of cooperation, increased dependency on others, and exaggerated invalidism. Not only do psychotropic drugs in these instances prove ineffective, but their side effects may be perceived as an additional burden which may often be confused with worsening of the underlying illness. These patients benefit from a great deal of participation by a concerned informed physician who meets with the patient and the family at regular brief intervals to stimulate participation of everyone concerned in bringing out untapped emotional and physical strengths of the chronically ill elderly invalid.

The emphasis of the meetings is on collaborative exploration of what the patient can do and on setting up simple tasks that can readily be accomplished by the patient. One such demoralized patient responded with a marked mood elevation after noting that he could squeeze a ball several times in succession just one week after a stroke. Problems which can be anticipated to arise in the near future should also be discussed always with emphasis on the patient's capacity and strengths. Patients should eventually be given the opportunity to talk about their reactions to their disabilities and about the changes that have occurred in their relationships with the significant people in their lives.

Common definable psychiatric illnesses that occur in this group of elderly cardiacs are endogenous depression and organic brain syndrome. The signs and symptoms of endogenous depression or of a major depressive illness are:

1. Depressed mood.
2. Psychomotor retardation or listlessness.
3. Difficulty in attention and concentration.
4. Inability to experience pleasure.
5. Physical symptoms such as anorexia, weight loss, constipation, insomnia.
6. Feelings of guilt and suicidal ideation.

Delusions of worthlessness, poverty, or body decay may also occur. Masked depression represents a variation of this syndrome and is manifested by excessive preoccupation with physical symptoms such as lightheadedness or nondescript pain. These symtoms or "depressive equivalents" are elaborated in a persistent and dramatic fashion, but depression *per se* is not evident either to the patient or to the doctor. This group of pathologic emotional reactions have a strong biologic component related to decreased catecholamines at the adrenergic receptor sites in the central nervous system. Tricyclic antidepressants are the treatment of choice.

Recognition of secondary depressions resulting from medications used in the treatment of cardiac illness is an important part of the differential diagnosis of depressive illness. Reserpine is the prototype of anti-hypertensive medication which may cause severe depression and suicide. The etiology of the depression is believed to be related to depletion of catecholamines and serotonin in the brain. In view of the incidence of depression, even small doses should be discontinued if symptoms of depression occur. A second frequent offender is Alphamethyldopa (7) which also produces functional depletion of brain catecholamines and serotonin through its action as a false transmitter. A sense of fatigue and malaise with a decrease in mental acuity occurs which may gradually evolve into a depression. Propanolol may also produce feelings of fatigue, insomnia, and mild depression, but their occurrence is relatively uncommon (8).

Depression may also be a presenting symptom of many physical illnesses, and careful physical examination should be included in any evaluation process. Harris (9) describes a 65-year-old man treated with electroshock for "mental symptoms suggesting psychiatric illness." The patient was described as drowsy and lethargic on admission. Diagnostic evaluation revealed chronic pulmonary emphysema, cor pulmonale, heart failure, and acute ventilatory failure. He responded to vigorous medical treatment and discharged "free from mental symptoms and returned to his regular work."

A second prominent syndrome in the geriatric cardiac patient is organic brain syndrome. This can be divided into chronic and acute states. We will focus our discussion on acute brain syndrome, since it is a commonly reversable disorder, and differential diagnosis of its etiology is important. Acute brain syndrome has also been referred to as delerium, acute confusional state, or toxic metabolic encephalopathy. This syndrome is characterized by the rapid onset of mental deterioration with mental confusion, disorientation, and altered levels of consciousness or awareness. Attention span is shortened and there is a tendency to wander rapidly from one fragment of thought to another. Perceptual disturbance may occur with misinterpretations of the environment such as illusions or visual hallucinations. Frightening dreams may overlap with hallucinations. There is an increase in psychomotor behavior with restlessness and bizarre movements, such as picking at the bed sheets or striking out at nonexistent objects. The diagnosis is established by the history of the acute onset of impairment in memory, orientation and attention span associated with perceptual disturbances and altered psychomotor activity. In the elderly cardiac, drug toxicity is a common cause of acute brain syndrome and may masquerade as senility. Any change in mental status associated with a new drug or increase in dosage should alert one to the possibility of drug toxicity. For the cardiac patient, the following medications warrant concern:

1) Digitalis. The usual sequence of Digitalis intoxication is nausea, anorexia, and visual disturbances such as blurring of vision and green, yellow, and white-colored vision. The cerebral symptoms which follow are headaches, excitement, impairment of memory, confusion, and delirium. De-

lirium occurs more frequently in elderly patients and in the presence of severe longstanding congestive heart failure. (10) Management consists of discontinuing Digitalis, vigorous medical treatment, frequent staff contact and, if necessary, the temporary use of restraints to control psychotic behavior, rather than excessive reliance on the use of psychotropic medication (11).

2) Quinidine. The primary manifestations of toxicity for this antiarrhythmic agent are: tinnitus, vertigo, blurred vision, and headache. Central nervous system symptoms include difficulty in speaking, confusion, excitement, somnolence, or delirium. Long-standing severe memory loss and confusion have also been reported (12).

3) Alphamethyldopa. This effective antihypertensive agent has been reported to decrease mental acuity resulting in forgetfulness and inability to concentrate (7). A toxic confusional syndrome with visual hallucinations has been reported for this drug when it is combined with the neuroleptic Haloperidol (13).

4) Propranolol. This peripheral beta receptor blocking agent has been reported to produce mild impairment of the sensorium, visual hallucinations and, on occasion, prolonged delirium (14).

Acute brain syndrome may also occur secondary to cardiac illness in the elderly. Congestive heart failure, especially if recurrent or longstanding, may result in a delirium indistinguishable from Digitalis intoxication. It may also be seen after acute myocardial infarction, cardiac arrest, or prolonged arrhythmia. Rapid changes in fluid distribution especially in patients who receive aggressive diuretic therapy for congestive heart failure may result in an acute confusional syndrome after the diuresis.

Another syndrome that must be given careful consideration by the clinician is pseudodementia. This term refers to the fact that an underlying psychiatric illness such as depression may mimic the chronic brain syndrome which is caused by degenerative brain disease. In mental status examinations, these patients may respond as though they were suffering from irreversible dementias.

Wells (15) has described a number of features helpful in distinguishing pseudodementia from dementia. In pseudodementia, for example, the onset of the illness can be pinpointed with some precision. A rapid progression of symptoms would suggest an underlying functional psychiatric illness. These patients respond dramatically to vigorous treatment of the underlying psychiatric order.

A 76-year-old man with a history of two heart attacks and congestive failure was seen on consultation for appropriate nursing home placement and management of his chronic brain syndrome. He did not appear to recognize people and had a paucity of movements and verbal interaction. A nurse's aide, while commenting on the patient's poor eating habits, noted that on occasion the patient demonstrated some cognizance of current events. Tests for depression such as the Beck Depression Inventory and the Hamilton Depression Scale were not helpful since he appeared unresponsive to questions. A trial of tricyclic antidepressants was unsuccessful because of marked anticholinergic effects and a course of ECT was given. The patient responded dramatically by the third treatment with an increase in the sense of well-being and activity on the ward and was soon discharged to be followed as an out-patient.

Management

The study by Chambers and Reiser (1) provides evidence of the need for a supportive approach to the elderly cardiac patient. In the group of patients who had experienced loss or rejection prior to admission, 17 were seen in the 48 hours after admission. This group demonstrated a strong need to ventilate emotionally charged material which was followed by "visible evidence of release and relaxation." There was a confessional quality to the interview with the development of a strong, positive attachment. Although many traumatic experiences were discussed including rape and death no patient developed congestive heart failure during these sessions despite the release of intense affect. In marked contrast, six patients seen after the 48-hour period demonstrated resistance to the interviews. They failed to develop a strong attachment to the doctor and gave poor histories regarding precipitating factors. The study was expanded to include five additional patients who had difficulty with recurrent episodes of congestive heart failure which were clearly precipitated by emotional factors. A decision was made to have these patients followed weekly by the same physician. It is noteworthy that this group of patients remained free of recurrence for the nine months of the study despite many of life's stresses. Three patients went into congestive heart failure two to seven days after the weekly visits were terminated. One rehospitalized patient commented, "I feel just as I felt just before you started taking care of me." From a psychiatric viewpoint, it would appear that the ongoing doctor-patient relationship satisfied the patient's dependency needs and consequently reduced emotional tension. The abrupt withdrawl of the physician represented another rejection to the patient. In ongoing psychotherapy, this rejection might be perceived as having triggered sufficient termination or separation anxiety to upset the delicate balance of cardiac function. Chambers and Reisers (1) indicate that patients seen within the first 48-hours were more likely to discuss the precipitating factors contributing to the hospitalization. The resulting positive emotional attachment is even more likely to develop in the elderly cardiac who lives alone or who has already endured many losses of friends and relatives. The doctor may become one of the few new and important relationships still available to the patient.

This study also corroborates the clinical orientation which stress the importance of developing good rapport and empathy toward the medically ill patient. This strong emotional bond will result in a dyadic relationship which is necessary to generate an anxiety-reducing, nurturant atmosphere. This nurturant atmosphere may result in a very powerful impact on mental functioning as evidenced in the "sundown syndrome." In the presence of a trusted staff member, patients with mild organic brain syndrome will remain mentally clear and alert and become confused when alone in the evening. A temporary impairment of cognitive function is attributed to the increased anxieties that develop from separation of close personal ties. A strong positive relationship may also diminish the reliance on medication or result in the use of lower doses of such psychotropics as anti-anxiety medication and major tranquilizers. In addition, the differential diagnosis of emotional disorders in chronically ill patients can be enhanced by strong therapeutic alliance. Distinguishing between demoralization and reactive or endogenous depression is aided by the response to the physician. Demoralized patients respond dramatically to close attachment and positive suggestion with a mood elevation within the first or second interviews. Patients with reactive depression, on the other hand, will often demonstrate a capacity to engage in dialogue with a good sense of humor only to become sad again when talking about their personal affairs. Often within two or three visits, however, these patients may abreact or release the painful effect related to loss, and the mood will begin to improve without the use of psychotropic drugs. Endogenously or psychotically depressed patients, on the other hand, have an unresponsive profound mood alteration. With a good rapport, the doctor is able to use himself as a powerful diagnostic and healing force rather than unnecessarily relying on psychotropic medication.

On the other hand, one must not hesitate to use somatic treatment if the depression is unresponsive to several contacts or is associated with life-threatening complications such as suicidal urges, marked anorexia, weight loss, or exhausting agitation.

In patients in whom the crisis has subsided, the physician may still maximize the development of rapport with interview techniques to enhance therapeutic alliance. In dealing with the elderly patient more time may be required. Take into account the patient's difficulty with hearing, seeing, and communicating. Be aware of the patient's cognitive defects which may potentially preclude a good response to an interview. If the patient perceives the pace to be too rapid, he or she may become anxious. The capacity to recall or give a good history is then diminished, and defensive withdrawal may ensue. Since one to three hours may be required to obtain the baseline data and develop a therapeutic alliance, it is helpful to have some guidelines of when to speak and when to listen. The patient is encouraged to respond at length to routine questions during the first three quarters of the interview. The focus of the discussion is on the nature of the presenting symptoms, but one is attuned to key words which reveal the patient's emotional state. Significant words used by the patient such as "draining," "difficult," or "empty," for example, may be reflected back to the patient in single word form, allowing the patient a moment to respond. On occasion, the response is a strong outpouring of short-lived emotionality. The interviewer should pace the interaction and attempt to maintain an interactive and informative tempo to help the patient feel productive. As the patient communicates freely, he or she begins to feel more effective, and self-esteem rises, anxiety decreases, and recall improves. Prolonged silence should be avoided since this will generate non-productive anxiety. Nonverbal communication of understanding and caring such as sitting close to the patient and touching him at appropriate intervals also encourages the communication of important information. Eye contact and a warm smile is helpful and conveys feelings of support and nurturance. Pay particular attention to the patient who concentrates a great deal on describing his bodily functions. As stated previously, many physicians demonstrate their annoyance with this type of behavior and label the patient as a "crock." This behavior may represent either a masked form of depression or a retreat from painful losses to the only reality he has, that is, the feeling of his bodily sensations. His preoccupation with bodily functions may become even more pronounced if the patient is isolated in his life. On the other hand, it may be his conception acquired from his family of what to talk about when visiting a doctor. The physician is encouraged to listen actively and show an increase in interest either verbally or nonverbally when emotionally charged material such as fear of death, loss of control, losses in relationships, or fears of the future are introduced. Discussion of these topics will often release painful effects and strengthen the rapport with the physician. It is particularly beneficial to reinforce the patient's recounting of pleasurable memories and activities since this is one of the most potent techniques to increase self-esteem and aid the remoralization process.

Ambiguity about treatment objectives are poorly tolerated by the elderly patient. It is important in the last quarter of the interview to summarize the historic data received, to discuss the diagnostic test that will be performed, and to plan the frequency and regularity of the meetings.

At followup visits, the quarter rule is applied, allowing the patient to set the pace, and reserving the last quarter of the visit to respond to questions, review previous laboratory findings, and to outline plans which are pertinent at that time. Length of stay in the hospital and post-discharge plans should be included early in the series of interviews. Advanced planning about discharge and appropriate follow-up care serves to reduce the likelihood of re-admission. In an effort to provide continuity of care, the patients in our after-care clinic are seen monthly for 20-minute visits. During this visit, changes which have occurred since that previous visit are reviewed, and any pertinent laboratory data explained. The remaining minutes may be spent discussing the outcome of difficult life situations or, hopefully, some source of satisfaction in their lives. In those occasional quiet interludes during the monthly visit, the therapist may fill in gaps in the social history to facilitate better understanding of the patient. A doctor-patient relationship will thus develop which may persist for a lifetime. Patients who are able to travel to the hospital despite their invalidism may benefit from participation in groups structured for the medically ill elderly patients. These groups, which may be conducted while they are waiting to see their physician, provide ongoing peer group support, avoid recurring separation and termination anxiety, and ensure a long-term commitment to care. This has been particularly helpful when medical and psychiatric house officers rotate at frequent intervals. We have formed a group for chronically ill patients who were characterized by their frequent medical admission to the hospital. This group of 12-15 patients has been meeting since 1972, and has had a 80% decrease in readmissions for medical problems. The bimonthly group meetings has had a 90%–100% attendance, and only three patients have died since 1972. Also of note was the same high attendance at the funerals of their fellow group members.

The Use of Psychotropic Drugs

It is not within the scope of this paper to provide a review of the use of psychotropic drugs in the elderly. There are certain guidelines, however, that should be considered in the comprehensive management of the cardiac elderly requiring psychotropic drugs. 1) Take a detailed drug review. 2) Start with low drug dosages and space increments in drug dosages at long intervals. 3) Observe the patient closely and more frequently when initiating drug therapy.

Drug review is particularly helpful in the geriatric cardiac when considering the use of a psychotropic drug. A drug review should include a discussion with family members and an accounting of all pills that have been prescribed for the patient. The patient on occasion will confuse one drug with another, that is, will take methyldopa for anxiety. Patients with poor hearing, vision, or forgetfulness are encouraged to bring all their medications to each visit. Secondly, drug review is essential to avoid drug interaction with drugs that have cardiac effects. Drug combinations such as those between clonidine and fluphenazine, haloperidol and methyldopa, guanethidine and most psychotropics, and lithium and diuretics should be avoided. The most important advantage of a drug review, however, is that it can help eliminate unnecessary medication. If a psychotropic medication is necessary, especially in the case of the tricyclic antidepressants and the major tranquilizers such as chlorpromazine or thioridazine, all anti-anxiety and sleeping medications may be discontinued. Tonics given to increase the appetite may also be discontinued. A helpful strategy in the management of mild to moderate hypertensives requiring psychotropics for depression is to discontinue the antihypertensive medication and to use antidepressants or major tranquilizers to control psychiatric symptoms and lower blood pressure. In patients with non-threatening arrhythmias, one should discontinue the anti-arrhythmic agents and use psychotropics which have a beneficial effect on arrhythmias, such as the tricyclic antidepressant, chlorpromazine or thioridazine. Anti-arrhythmic agents, however, should not be combined with tricyclic antidepressants or with the major tranquilizers of the low potency group such as chlorpromazine or thioridazine. Drug review might also point out certain areas of incompatibility. In patients with cardiac conduction defects and/or active coronary artery disease, one should be very careful with all tricyclic antidepressants with the possible exception of doxepin. Patients with a current or past history of congestive failure should be brought under complete medical control to ascertain that the depression is not secondary to cardiac illness. In prescribing tricyclic antidepressants for the depressed patient with a history of congestive heart failure, their negative inotropic effects should be taken into account to avoid precipitating failure (16). It is wise to get a baseline weight and/or vital capacity before beginning the medication and to observe the patient carefully for weight gain after initiating drug therapy. An ideal drug review would result in a regimen in which one medication is given once every evening for treating a mild hypertensive patient who is anxious and depressed and has sleeping difficulties and occasional episodes of palpitations. This reduced dosage results in increased compliance with the drug regimen.

Low beginning doses of cardiac and psychotropic medications are recommended in the aged. They are not only more sensitive to drug side effects, but drug absorption, distribution, metabolism and excretion are decreased with potential doubling of the mean half-life of most psychotropics. For example, the measurement of tricyclic antidepressant blood levels in this group of patients demonstrates unpredictably high blood levels on small doses of medication (17). Cardiacs especially with a history of congestive failure may experience exaggerated difficulties with drug distribution and excretion. Therefore, the caution of small initial doses should be accompanied by a longer period of observation prior to increasing drug dosage.

An example of the effects of both age and illness on drug tolerance is demonstrated in the following case. A 72-year-old man was treated seven years ago for endogenous depression precipitated by his retirement. He responded in ten days to Imipramine, 75mg for three days with stabilization on 150mg daily dose. He had no significant orthostatic change in blood pressure. Four years later, he had a small stroke and an episode of congestive heart failure secondary to arteriosclerotic heart disease. Treatments for his current depression with the same drug regimen was unsuccessful because of marked orthostatic hypotensive response to 75mg of Imipramine daily. The drug was reduced to 25mg at bedtime with the usual caution of getting out of bed slowly. At a nightly dose of 50mg, his blood pressure went from 160/94 to 120/70. His blood pressure stabilized at this level and a antidepressant effect was evident in three weeks. Thus, close and frequent observation is required when initiating drug therapy and with each new increase in dosage. Troublesome side effects may not only be pronounced, but also their onset delayed because of absorption and distribution difficulties.

In summary, effective diagnosis and treatment of the elderly cardiac patient requires a comprensive biopsychosocial approach. In no other group of patients is George Engel's model of illness so appropriate or essential (18). Appropriate and timely use of psychotropic medication for the geriatric cardiac patient is, of course, important, and awareness of drug-drug interactions and side effects can avoid atrogenic difficulties. However, of equal or greater importance for these patients, we have often suffered significant losses, is the quality of the relationship between themselves and their doctor. Once the physician is able to overcome his own biases and fears about aging, as manifested in the defensive maneuvers of gerontophobia and selective inattention, he is then in a position to use himself as a therapeutic agent, thereby improving the patient's quality of life.

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Social Research on Aging and the Aged: Where Are We Now?

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In 1975, a paper was presented at the International Association of Gerontology meetings in Israel entitled "Gerontology and the Social and Behavioral Sciences: Where do we go from here?" It seems appropriate to use the present occasion to indicate first, where we are in social research in aging and secondly, the direction in which we seem to be going.

Important social and behavioral research in aging has advanced in a variety of fields concerned with the interrelationships between human behavior, social structure, and social institutions. We can now point to research on aging and the aged in anthropology, architecture, developmental psychology, economics, health care services, human geography, political science, population research, sociology, and town planning among other social sciences. It is not possible to report on the status of research in all these fields. Therefore, the limited topics discussed here were chosen from the program emphases of the social and behavioral research program of the National Institute on Aging of the National Institutes of Health. This program supports research on 1) older people in the changing society, 2) psychologic and social components of the aging process, and 3) older people and social institutions. The specific interests of the National Institute of Aging and its staff in each of these categories can best be summarized in their own words. Thus, the program on older people in the changing society—

> "Supports research on the age composition of the population; patterns of rural and urban migration; morbidity, mortality, causes of death, and problems of dying; and age-related inequalities in income, labor force participation, voting, housing, transportation systems, and education. This category also stresses such topics as reduced economic dependence of parents on adult children, changes in mandatory retirement ages, and estrangement of older people from the dominant popular culture."

The program on psychological and social components of the aging process—

> "Oversees studies of perception and sensation, psychomotor skills, cognition and intelligence, memory and learning, and creativity and wisdom. This category includes social psychological studies of personality traits, attitudes, self-image, sex role differences in aging, socialization and interpersonal relationships over the life course."

The program on older people and social institutions—

> "Research involves the relations of aging individuals to the social institutions within which they grow old. For example, studies might explore how the family, peer groups, kin networks, and economic, religious, legal, educational, political, health and leisure institutions can shape older people's lives and, in turn, be shaped by older people."

Older People in a Changing Society. The contributions of demography and demographers to our understanding of the elderly are often overlooked. That there are many elderly people in this country and elsewhere in the world is generally accepted. Using a calendar definition of old age, demographers tell us that there are now 24.5 million persons in this country aged 65 and over and that they comprise one of every nine Americans. This so-called aged population is itself growing older. The ratio of the "young-old" to the "old-old" is shrinking in size. In 1975, there were already 49 persons aged 80 and over for every 100 persons aged 60 to 64 (Siegel, 1976). Put another way, there were two 60-year-old youngsters for every oldster, aged 80 and over. These very old persons, well beyond the Biblical three score and ten, continue to increase in number. To illustrate, there are now more than 2 million Americans 85 years of age and over (Siegel, 1976). It is difficult to visualize 2 million people. For comparison purposes it may help to recall that only three of our largest cities, New York, Chicago, and Los Angeles, have more than 2 million residents. Since no one has yet figured out a way in which we can remain vigorous as long as we live and turn off at just the right moment, it is from this "city" of 85 years and older persons that we recruit the majority of our nursing home and institutional residents.

Demographers have pointed out the difference in life expectancy between whites, Blacks, and other races. Even more relevant for us here, there is an amazingly similar life expectancy of all persons irrespective of race who survive to age 65. Despite improvements in health care and health behavior, the average expectancy of life at birth of both white males and white females continues to be greater than the expectancy of life of Blacks and other races. At birth, the average white male baby can now expect to live 69.7 years, compared to 64.1 years for the male baby born to mothers of Black and other races. The average white female baby can expect to live 77.3 years compared to 72.6 years for the female baby born to Blacks and other races. However, the older the population cohort, the less the racial differences in length of life. In 1976, white males who survived to 65 could expect to live another 13.7 years; males of Black and other races, 13.8 years, white females at 65 could expect to live another 18.1 years; females of Black and other races, 17.6 years (U.S. Bureau of the Census, 1979). Indeed, among those who reach the age of 80, about 54 percent of white men and 68 percent of white women will reach 85; but among Blacks and other races, even higher proportions (63 percent of men and 73 percent of women) will reach age 85 (Kovar, 1977).

My own work in estimating the physical mobility and the capacity of self care of white and Black elderly is relevant here. At ages 65–69, Blacks compared with whites are much more limited in mobility. Blacks are much more likely, for example, to say that they cannot walk stairs, or that they cannot go outdoors without help. But, by ages 80 plus, the limitations in physical mobility and the capacity for self-care reported by white and Blacks are about the same. The over 80's, irrespective of race, become more alike physically (Shanas, 1980b). The data suggest that survival to an advanced age overrides these racial differences which may be the result of different cultures and life experiences. Basic biologic similarities which make for longevity seem to become more important than social and cultural factors as determinants of physical functioning.

Psychological and Social Components of the Aging Process. The recent contributions in the fields of psychology and social psychology to our knowledge of aging are enormous. For those who are not psychologists, I need only mention that the American Psychological Association has just published a 636 page, double-column, volume, under the title "Aging in the Eighties, Psychological Issues."

The major psychologic studies of aging stress 1) the enormous variability among older people of the same calendar age, 2) the need for assessment instruments to measure various aspects of the psychology of aging, and 3) the contributions of life span studies.

Calendar age is a poor indicator of how well older people function. Study after study has demonstrated the variability among persons of the same age on such items as measures of intelligence, learning, et cetera. The physical appearance of people also is little related to their calendar age. Each of us has observed the differences in appearance of people of the same age. Some look "old for their age," others, "young." Yet despite these obvious differences, which are reinforced by studies of psychologic and physical capacities, we continue to make categoric statements about "the elderly," using calendar definitions.

Assessment studies are part of the tools of the trade of psychologists. Investigators in aging have become increasingly sophisticated in their use of such tools. They have demonstrated that scales and other instruments standardized on the basis of younger age groups are often not relevant for the elderly. This may seem obvious now but for many years such scales were used in studies of the elderly. Further, psychologists are placing increased emphasis on the development of multidisciplinary measurements of function. In the American Psychological Association publication referred to earlier, a review article speaks of "the need for integrative multidimensional approaches to minimize the high probability to misdiagnosis when the perspective and tools of only one discipline are used" (Gallagher, Thompson, Levy, 1980).

The findings of prospective life span studies of the same persons as they age, perhaps have made the most important contributions to our understanding of the psychology of aging. Such studies have resulted in a reevaluation of the evidence on intellectual aging. It is now apparent that intellectual aging is much more plastic and heterogeneous than past research would have implied (Willis and Baltes, 1980). Abilities are not fixed but can change both positively and negatively through the life span. Such studies have also demonstrated that while there are declines in physical functioning with age, there is often no decline in social and psychologic functioning. Overwhelmed with problem "cases" and persons in need of care we tend to forget that most normal aging persons continue to function within the community. Their behavior does not necessarily change with the turning of a leaf on the calendar.

Life span studies also have demonstrated that the individual's past is significant in the explanation of behavior exhibited in middle age and aging. Again, we may say "But everybody knows that!" However, everybody does not know "that," or act upon this knowledge. Coping or adaptive styles developed earlier in life continue to be used in later life. Lazarus and his colleagues at Berkeley have shown that the way people appraise a situation, an appraisal based on past experience, has important consequences for the way they cope with that situation (Lazarus, Averill and Opton, 1974).

Investigations focussed on the isolation of personality types in old age, a major theme in psychology, strongly reflect the orientation developed in life span studies of middle age and aging (Neugarten, 1964; Lowenthal, Thurnher, and Chiriboga, 1975).

Older people and Social Institutions. None among us live in a vacuum. The institutions of our society, familial, economic, political and religious, all affect our lives. Although demographic analyses tell us that we in the United States are collectively growing older our social institutions are oriented toward youth. "We deprive older people of work, their major source of income, and thus make it impossible for them to compete for goods and services in the marketplace. For older people who prefer not to work forever, and they are the majority, we downgrade their leisure-time activities and view them as trivial. We accept in the young, modes of behavior we condemn or at least frown upon among those in the middle or later years. Barefoot college students on the street do not draw a second glance; barefoot older persons are considered, at best, eccentric and, at worse, mentally incompetent. . . . Despite the fact that the men sent to the moon were middle-aged (because, in that strange environment, experience and judgement were deemed to be of utmost importance), we continue to downgrade attributes such as theirs in those we describe as 'old'" (Shanas, 1980a). For many persons, older people are somehow set apart from the stream of adult life. They are not really accepted as adults with "full status" like the middle aged. Rather they are "seniors" and as such they differ in kind from other adults.

The integration of older people into society and how older people relate to social institutions have been major research themes of the past decade. The most significant of this research has been in the area of familial relations. Indeed, the 1980 meeting of the Gerontological Society (chaired by Elaine Brody) was organized around the theme of the "Family." I shall report some of these findings about older people and their families shortly, but first I should like to say something about some research findings dealing with isolation among the elderly.

Family relationships and isolation are often presented as though they were on the same continuum or axis of content. I consider this to be an error. The isolated person can be described as someone who suffers from feelings of loneliness and feelings of alienation, and who desires more interaction with other persons than he or she may now have. Many of the discussions of isolation among the elderly assume that persons living alone are isolated, and that somehow were these persons to live with others they would be less isolated. Living alone is not necessarily a concomitant of isolation. Many older persons living alone, like many younger persons, are neither lonely nor alienated. They feel no special need for more interaction with other persons. Individuals, whether young or old, differ greatly. Situations which one person might find distressing and conducive to feelings of loneliness, might be accepted by another person as quite usual and nonstress producing (Tunstall, 1965). The psychic feelings of the person and the nature of his or her interaction with other persons may be more important than living arrangements in identifying the isolated elderly.

Data from a 1975 national survey of the noninstitutionalized aged indicates that about three of every ten noninstitutionalized older persons live alone. The proportion of old people who say they are often alone is also about three of every ten but those who say they are often alone are not necessarily the same persons as those who live alone. For example, about a third of all widowed parents in the same household with their children say they are often alone. Obviously, these persons are not physically alone, they are "alone" for other reasons.

From six to nine percent of those living alone, something less than one of every ten of all older persons, said they had no interaction with other persons on the most recent weekday or the Sunday before the interview. These seem to be "isolated" persons. However, these persons were the exception among those living alone. Most persons living alone reported visiting with friends, at the home of these friends, neighbors or relatives.

The isolated aged while small as a proportion of the total aged, perhaps one in ten, are large in number, about 2 million. Further, they are not randomly scattered throughout the population. They tend to cluster in sections of our large cities and in "old" suburbs. They are probably more likely to be found in New York or Chicago than in an American small town.

Children are the major social support of aged parents whether or not the generations live together. About two of every three persons living alone were the parents of children. About half of these elderly parents living alone (one of every three persons living alone), lived within ten minutes journey or less from their nearest child; four of every five (almost two of every three persons living alone) lived within an hour's distance of a child. About half of all parents living alone saw at least one child the day they were interviewed or the day before that, three of every four had seen at least one child during the past week.

The proportion of old people living in the same household with one of their children has declined as the income of old people has risen. In 1975 about 18 percent of older parents lived in the same household as a child. Thirty-four percent of older parents lived apart from their children, but within ten minutes of at least one of them. These parents include elderly couples as well as widowed and divorced parents living alone. Overall, half of all people with children (52 percent), lived either in the same household with a child, or next door, down the street, or a few blocks away (Shanas, 1979). Further, older parents and adult children not only live close to one another, they see one another regularly and often. Three of every four parents saw at least one of their children during the week before they were interviewed.

Relatives other than children also play an important role in the family life of old people. Old persons who have never married are especially likely to be close to their brothers and sisters. Many live in the same household. While only one-third of all persons with siblings had seen a brother or sister the week before they were interviewed, among those who had never married, three-fourths saw a brother or sister (Shanas, 1979). In addition to visiting with children and siblings, old people visit with other relatives who are not among their direct descendents. About three of every ten older persons said that they had seen some relative who was neither a child, a grandchild nor a brother or sister during the previous week.

We know very little about the quality of the interchange either in the households shared by older people and their adult children or in the visits between older people and their children and other relatives. Old people living in the same household with children or relatives may find such an arrangement satisfactory or they may find it unpleasant. In a national survey made some 20 years ago, those older parents who lived in households separate from their children were the most likely to oppose living with a child; those already living in the same household with a child were the least likely to oppose this mode of life and to say that this is the preferred living arrangement for older people (Shanas, 1962). I would guess that we would find much the same attitudes about living arrangements among older people were we to repeat these questions today. People tend to approve of the living arrangement in which they find themselves. Similarly the visits between older parents and adult children may be fraught with hostility or they may be warm and supportive for both generations.

About four of every five of the noninstitutionalized elderly have living children. The old person with children has had different experiences than his childless contemporary. The person with children is not only a parent; as a parent, he is part of a lineage. Often he or she is the beginning of a lineage of three, four or even five generations. Almost half of all persons aged 65 and over in this country who have living children are members of four-generation families. The likelihood of being a great-grandparent increases with age, and among those 80 and over, almost three-fourths are great-grandparents. On the other hand, there are great-grandparents among the "young-old" too. One-fourth of those aged 65 and 66 in 1975 are already great-grandparents (Shanas, 1978).

I have called these old people and their families the "new pioneers of our era." Old people and their middle-aged children have ventured into uncharted areas of human relationships, and developed systems of exchange and interaction without help or guidance from the so-called helping agencies in our industrial society. Astronauts and space vehicles have sophisticated guidance systems. Old people and their families have only those traits which distinguish human beings from other animals: love, sympathy, and the ability to emphathize one with the other. The family—spouse, siblings, and other kin—serves to integrate old people into society. The four-generation family, plagued as it is with role ambiguities, supports its members with informal as well as formal help (Shanas, 1980a).

I turn now to a brief discussion of some of the implications of recent social research findings on aging in demography, in psychology, and in the analysis of the aged and social institutions.

It seems obvious that we must begin to disaggregate data, to cease viewing the aged as a homogeneous mass. The heterogeneity of this population, the differences between the "young-old" and the "old-old," the differences between races and the differences between various cultural groups is obvious. These differences must be kept in mind in the design of research and the analysis of research findings. There is a need for studies which relate biology to social behavior. This area of emphasis, which is most apparent in certain of the life span studies in aging, particularly in the longitudinal studies at Duke University, emerges as a strong direction for research in the '80's. Why, for example, among the reported findings of research, do Blacks, with a life expectancy at birth which is less than that of whites, if they survive to age 80, outlive whites? Why do some people develop coping styles which are adequate in old age, while others either cannot develop such methods of coping or find their coping styles inappropriate to their life situations? There has been a good deal of research on measuring stress. Are what Richard Lazarus calls "hassles" more stressful for older people than major life events, and, if so, why?

There is a need for better measures of outcomes, not only the outcomes of psychologic tests, but of medical treatment. At this time the usual measure of success or failure of medical treatment of the aged is mortality—a very poor measure when much of such medical treatment is devoted not to keeping people from dying but to making people who have chronic ailments which cannot be cured feel better. Is how these patients feel an unimportant outcome?

The whole area of family and kin relations in old age needs further investigation. Our dominant culture stresses independence whereas research shows that life in old age is marked by the "interdependence of the generations." Often such interdependence can only be achieved by sacrifices on the part of both the middle-aged, the young, and the old. What does it mean to an old person to be part of a lineage, and what does it mean to reach old age and have no survivors?

In general, it is my belief that the research questions in aging in the social sciences for the next decade will more and more deal with areas which integrate the biologic and social aspects of behavior. Both biology and the social sciences will have to learn more about each other. This sharing of knowledge of different disciplines can serve to enrich each of them.

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Workshop I (*Part a*) Research in Clinical Medicine in the Aged

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Workshops

Editor's note: Because of the amount of material presented in this two day symposium, we have briefly summarized workshops 1–4. We regret that we could not fully present these workshops with all details complete.

A discussion of research in clinical medicine in the aged requires the evaluation of questions such as: what are the objectives, how can medical students, house physicians and practitioners be motivated to involve themselves in such research, where should clinical research be carried out, how can it be funded, what have been the significant recent contributions of such research, and what fields have a potential for further exploration?

The objective of clinical research in the aged is answering the patient's questions "what is wrong with me and what can you do about it?" Therefore it is intimately related to clinical practice and social conscience.

It is a form of applied science and, as a result, suffers from a dangerous form of snobbism in science which draws distinctions between pure and applied science.

A dedicated clinical scientist must learn to disregard those scientists who say that he is not a proper scientist and those clinicians who say that he is not a proper clinician.

To foster clinical research in the aged, programs in gerontology and geriatrics in the medical school and in the house staff training are needed. The general hospital and the medical school have an opportunity to coordinate their teaching and research activities with affiliated chronic care institutions, homes for the aged, home care programs, and community centers for the aged, particularly those located in housing projects for the aged. Through such exposure, students, house physicians and members of the attending staff may decide to do clinical research among the aged.

A chronic disease institution which is adequately staffed, with adequate diagnostic and therapeutic capabilities, and whose population includes a broad spectrum of functional capacities—from the fully ambulatory to the chronically ill—is an ideal site for long term longitudinal studies of the aging process and disease. Clinical research on the well aged is of the greatest importance. Past studies confined to the hospitalized aged have yielded distorted results regarding a number of conditions.

Clinical research in the aged can be stimulated by small grants to medical students and house physicians. Governmental funding sources and private foundations should give more recognition to funding research in community centers, institutions for the aged, unaffiliated clinics, and community agencies dealing with the well aged. Voluntary attending physicians can play a valuable role in conducting such research.

The value of relatively small expenditures in supporting research is evident. Insulin replacement therapy for diabetes cost only $15,000 from the onset of the idea, to the delivery of the first insulin for injection into humans. Polio vaccine cost a total of $41 million to develop and test and has saved 70 times that amount in medical costs each year of its use.

In 1977, $4,500.00 was spent for research in chronic brain disorders while six billion dollars was spent for nursing home care for such conditions.

The present trend away from human centered

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and disease oriented research and the concomitant increase in investigations whose material is neither human nor diseased, has been documented by Feinstein and Kass (1).

In an analysis of the abstracts submitted to the annual meetings of the American Federation for Clinical Research, the American Society for Clinical Investigation, and the Association of American Physicians, between 1953 and 1967, they found a long term decrease in human disease research and an increase in the nonhuman studies. Between 1965 and 1967, about 2% of the research papers submitted to the subspecialty sections were patient centered (1).

Booth, in 1980, demonstrated a similar trend for the years 1974-1979, with a progressive marked decline in the number of clinical scientists both here and in England and their replacement by nonmedical scientists usually holding a Ph.D. degree (2).

In the aged, a reasonable balance of types of medical research is desirable. Excess emphasis on nonhuman, nondisease studies results in the alienation of the investigator from human problems.

Clinical medical research in the aged should result from and lead to good medical care, and should be based on the premise *primum non nocere.*

Informed consent is a difficult problem in research in the aged, particularly among those in long term care institutions and in hospitals. The determination of adequate cognitive ability to yield such a consent from those who are chronically ill, who are heavily medicated, and who have varying degrees of fluctuating senile dementia, both chronic and acute, is difficult.

The attempt to evaluate a degree of cognitive ability sufficient to consent with adequate information and understanding of what is involved by psychologic tests, in many cases, causes more stress than the procedure for which the consent is sought.

It has been questioned whether institutionalized persons can give truly voluntary consent or not. Patients become emotionally dependent on the caregivers which limits their ability to resist demands upon them. Many patients would consent to anything suggested. Obtaining consents from guardians is difficult since the law prohibits them from approving research if there is no possible benefit to the subject. Even research with "minimal" risk defined as the "probability and magnitude of physical and psychological harm that is normally encountered in the daily lives or in the routine medical and psychological examinations of healthy subjects," would come into question if there was no necessary benefit to the patient. There is a need for new legislation to overcome these difficulties preventing meaningful research on the vast problem of senile dementia (3).

A recent study of mentally clear individuals, 20 to 82 years of age, has found that on testing for the recall of the significance of the informed consent within one day of signing, only 60% understood the purpose and nature of the procedure and only 55% correctly listed even one major risk or complication. The more ill the person the worse their comprehension (4).

The questions also must be answered as to whether human research committees inhibit clinical research and to what extent. It is possible that the increase in animal research and decline in human research, in part, reflects a feeling that it is easier to do animal experiments than to go through the paper work and committee proceedings of human research committees (3).

There are a host of conditions about which we know very little. As an example, there is no agreement about the etiology or evolution of calcific aortic stenosis, a common and important condition. Cross sectional studies of the present generation of aged individuals are of limited value due to secularity, since the subjects were born long before 1900 and brought up under different medical, social and economic conditions, often on another continent.

Cross sectional studies of a variable which is related to survival, either because it is a risk factor or has a protective effect, will result in what appears to be an age related difference which does not exist. For example, a high cholesterol level has an adverse effect on mortality. Therefore, comparing the aged survivors of a group of whom those with a high cholesterol have died more frequently than those with a low cholesterol, and those who are 30 to 40 years of age, will inaccurately suggest that the cholesterol level declines with age. In a longitudinal study of a prospective type, this effect will be absent or greatly diminished (5).

Long term longitudinal studies, that follow up younger individuals by periodic multi-phasic evaluations to necropsy examination are superior, especially since only in this way can the rate of change of specific functions be assessed for any given individual. These studies have inherent disadvantages of costliness, attrition of subjects due to death, lack of interest or relocation, the saddling of the investigator with outmoded methods, and the necessity for recruitment of young staff members who can be expected to outlive the subjects and carry on work begun by older investigators. The introduction of additional newer diagnostic techniques during the course of such studies will add to their value.

The establishment of normal values for the aged is important. We accept without question that infants, children and adolescents have a changing spectrum of normal values over a period of about seventeen years. Yet, we tend to accept normal values for adults as valid for the aged over a span of up to thirty-five years after age 65. We are just beginning to realize how difficult it is to establish normal standards for the aged even in such extensively investigated conditions as diabetes mellitus. There is no unanimous opinion as to the definition of normal glucose tolerance in the aged.

Research, establishing normal values by ascending age for pulmonary function, is valuable and encouraging. It shows that if a heavy smoker stops smoking, his pulmonary function returns to normal within 18 to 24 months. During the smoking period their pulmonary levels are those of an individual ten years older (5).

A pitfall in determining normal values in the aged is demonstrated by the creatinine clearance test, whose 24-hour value is used as an index of the glomerular filtration rate and of renal function. In the aged, a parallel decrease occurs in creatinine clearance with aging and with daily creatinine excretion caused by decreased muscle mass. The net result is no change in serum creatinine level.

The significance of the blood pressure level of any given aged individual is difficult to assess, since it is the result of a number of factors related to aging and disease, such as decreased elasticity of the great vessels, dilatation of the aorta, and a rise or fall in cardiac output, as well as the arteriolar constriction of essential hypertension.

There is ample opportunity for future clinical research in this field, since studies are needed to determine indications for treatment with antihypertensive drugs and optimal treatment regimes. The efficacy of treatment will be judged by the results of morbidity and mortality studies. While combined systolic and diastolic hypertension are significant risk factors and require careful therapy, the value of treatment of systolic hypertension in the aged is not established. Long term prospective studies are needed.

In the mass enthusiasm for determining and treating risk factors for coronary artery disease in the American population, little attention has been paid to their significance in the aged.

Recent studies on serum lipids, obesity, cigarette smoking, personality type, diabetes and hypertension in the aged have revealed findings that require further investigation. These studies have been analyzed in a recent publication(6).

Obesity of moderate degree in a multitude of studies has been found not to be a risk factor for coronary heart disease, either for initial or subsequent attacks in the aged. In fact, the aged who are mildly to moderately overweight have a better life expectancy than those of normal weight or those who are underweight.

The reasons why total cholesterol is no longer a risk factor in the aged need investigation. High density lipoprotein cholesterol in younger individuals is a favorable risk factor for coronary heart disease particularly when the ratio of total cholesterol divided by HDL cholesterol is low. A high level of low density lipoprotein cholesterol is unfavorable. Whether these factors apply to the very aged is not known. More importantly, can we significantly affect these parameters by treatment with a decrease in the incidence of coronary heart disease?

The value of exercise programs in preventing and reducing mortality from coronary heart disease remains to be established. Alcohol's overall effects in the aged are not clear. Its use is associated with a decreased mortality from coronary heart disease, but with a greater death rate from other causes in younger age groups.

Supposedly, cigarette smoking is not a coronary heart disease risk factor in the aged, but there are no definite results to this effect. However, its effect on overall mortality in the aged is unfavorable.

Type A personality is not regarded as a risk factor in the aged. What is needed is a study of whether such personalities live to be aged and whether there is a change in personality with aging. With aging, women have been found to become more aggressive and men more passive (6).

The difficulties inherent in epidemiologic research at any age are illustrated in a recent article by the Coronary Drug Project Research Group.

The efficacy of clofibrate in reducing mortality over five years in over 1100 men who were treated was compared to over 2700 placebo cases. There was no difference in mortality. When good adherers to the therapeutic regimen were compared to poor adherers, there was a similar reduction in mortality in the clofibrate and in the placebo group. This may be an expression of the different personality types in adherers and nonadherers over a wide spectrum of life style (7).

Research by means of long term prospective randomized trials is needed to establish the effects on morbidity and mortality of these risk factors in the aged. Are the adverse effects of medication and strict diet, exercise and inhibition of pleasurable activities such as smoking or eating, more than overcome by the beneficial effects of the therapeutic regime?

Because a risk factor is positive for coronary heart disease does not mean that removing the risk factor will remove its adverse effects or not induce others as is the case with clofibrate with regard to gallstones. Alcoholics have less coronary artery disease deaths but more deaths from other causes.

The successes we have achieved in reducing the mortality from ventricular tachyarrhythmias in acute myocardial infarction should not obscure our failure to reduce the extremely high mortality from cardiogenic shock in this condition, particularly among the aged. Clinical research is needed to determine the etiology of cardiogenic shock in the hope of discovering improved methods of treatment. Drugs such as dopamine need to be evaluated. With new simplified techniques of intraaortic baloon pumping, using a percutaneous technique, this method which has not been used in the aged may be evaluated.

After 30 years of investigation and hundreds of clinical reports, no definitive statements can as yet be made about the value of anticoagulants in coronary heart disease. Resolution of this problem is of special urgency for the aged, since therapy in them is more hazardous because of an increased sensitivity to anticoagulants, resulting in a susceptability to cerebral and intestinal bleeding.

The etiology of heart failure, the end point of so many aging hearts, is not completely understood. In some respects, our thinking is not ahead of that of Thomas Hobbes who, in the 17th century, regarded the heart as a spring and the failing heart as a worn out spring. Much research remains to be done to discover what happens to the aged myocardial fiber which causes it to fail, independent of disease.

The present therapy for heart failure leaves much to be done in the way of clinical research. Our knowledge of digitalis, still the most important form of treatment, has in many respects not, until recently, advanced much beyond that reported by Dr. Withering in his Account of Foxglove in 1785 in which he said, "despite opinion, prejudice or error, time will fix the real value upon this discovery" (8). Time has confirmed the value of digitalis in augmenting the contractility of the normal and the failing heart (9), but has not solved the problem of its narrow toxic therapeutic ratio which results in an incidence of 7% to 22% of toxicity in hospitalized patients, particularly the aged, receiving digitalis derivatives (10).

Recent research has shown the value of vasodilator therapy in controlling acute heart failure by reducing preload and afterload. Drugs such as hydralazine and prasozine reduce afterload by causing arteriolar dilatation. Nitroprusside, nitroglycerine and prasozine reduce preload. Long term therapy of this type in chronic failure has been reported. The value in the aged of such therapy over a long term and the possibility of relapse after cessation remain to be established.

The value of newly investigated drugs such as verapamil and nifedipine which block the slow calcium channel of cardiac muscle contraction in relieving coronary artery spasm with consequent variant angina at rest, must be established in the aged as is their value in paroxysmal atrial tachycardias. Research has shown that the coronary arteries of the aged which were not supposed to be able to constrict because of atherosclerosis and loss of elasticity, do constrict and produce variant angina. Myocardial infarction due to a loss of blood supply rather than increased cardiac work may occur. In other words coronary artery spasm yields an impaired blood supply without the increased left ventricular wall tension and rise in blood pressure seen with increased cardiac work in typical effort angina.

Only in the recent past have we begun to understand the mechanisms of action of digitalis through research studies of its metabolism and excretion using radioactively labelled digoxin, radioimmune assay and red blood cell rubidium uptake inhibition methods (10).

Studies using radioactively labelled digoxin, show that there is an initial accumulation of digoxin in the body when small doses are given daily. However, as the amount excreted each day is one third of the total amount accumulated in the body, the amount retained each day increases until an equilibrium of absorption and excretion is reached on about the sixth day, at which time there is an effective dose present in the body. Utilization of this method of digitalization in nonemergency situations will reduce the incidence of digitalis toxicity in the aged (11). Researchers have also demonstrated the direct relationship between digoxin excretion and renal glomerular filtration rate. Since the latter is only one half of the normal rate in the aged, digoxin is excreted less rapidly, indicating the need for a substantial reduction in maintenance dosage (11). Research has demonstrated that intravenous injection of the same dosage of digoxin will yield twice the blood level in a small aged person as in a large young person. Thus, digitalis sensitivity in the aged may be explained not only by low body potassium and magnesium but by decreased body size, muscle mass, and renal glomerular filtration (11). These encouraging advances indicate how clinical research can help in providing improved treatment for the elderly cardiac.

Clinical research has demonstrated that the combination of digoxin and quinidine leads to a very marked increase in digoxin level and often toxicity. This is similar to the research that revealed most generic forms of digoxin yielded unpredicatable low serum levels.

New techniques of continuous monitoring of the heart by electrocardiographic telemetry are valuable aids for research for study of the effects of stress on the heart, such as automobile driving. This technique has shown that episodes of syncope and faintness, otherwise unexplained, are often due to brief periods of brady or tachy arrhythmias.

In a series of 59 patients with complaints of dizziness, syncope, palpitations and falls, average age 82, Gordon found 16 with related diagnostic arrhythmias. Twelve of 16 had resting electrocardiograms with no findings suspicious for the arrhythmia found on ambulatory monitoring. Medical therapy controlled the arrhythmia in eight. However, a temporal correlation must be established between the occurrence of the arrhythmias and the clinical symptoms since arrhythmias are common in the asymptomatic aged (12).

Such research is of great value to the patient therapeutically and represents a financial benefit because, when positive, it obviates the need for time consuming and expensive procedures such as computerized axial tomography, electroencephalograms and elaborate vestibular testing.

The introduction of intracardiac pacing techniques and electronic pacemakers have prolonged the life span of aged individuals with heart block and present opportunities for future research. The introduction of graduated small amounts of electric current in different locations within the heart and at different time intervals in the cardiac cycle have elucidated the significance of the vulnerable and supernormal phases of the cardiac cycle during which an ectopic beat may trigger a fatal arrhythmia, particularly in the course of acute myocardial infarction.

Previously, inaccessible portions of the conduction system of the heart such as the Bundle of His and the Bundle of Kent can now be studied. Surgical therapy of the W-P-W Syndrome is now possible. We will learn more about the genesis of the potentially preventable ventricular arrhythmias which cause over half the deaths from coronary artery disease (13).

The technique of exercise testing has demonstrated that 38% of well aged males have an ischemic response to exercise compared to only 4% of healthy young males (14). Such modaliteis of research will help in the determination of the benefits of physical conditioning.

Modern research has found much of interest about the aging heart. Angiocardiography is performed using a gamma camera when radioactive technetium is injected into the jugular vein during bicycle exercise and at rest. Data were stored on magnetic tape and processed by a computer. It was noted that at rest, age did not affect the left ventricular ejection fraction, end-diatolic volume, and regional wall motion. Age, during exercise was related to significant declines in those over 60, in all three parameters with progressive decline with aging in the incidence of wall motion abnormalities. Maximum heart rate and oxygen consumption also decline linerarly with age as do maximum stroke volume and cardiac output (15).

A new and fascinating example of recent complex cardiologic research has just come to fruition after work on dogs. This is the perfection of a method of terminating ventricular fibrillation and flutter, the chief cause of sudden death in this country, probably a million deaths a year. Lead wires are inserted into the heart as with a pacemaker from the implanted electronic mechanism, which senses the onset of the arrhythmia by analysing the electrocardiogram. It then stimulates the heart with 25 joules of current, a small dose compared to the similar stimulation of the heart by external direct current electroconversion of up to 400 joules for atrial and ventricular arrhythmias. The mechanism recycles itself and can give repeat impulses three times if necessary. The patient feels very little pain or discomfort such as palpitation. The unit can function for three years or approximately 100 impulses (16).

It is essential to give attention to research in cancer in the aged. Despite the availability of a large number of cytoxic agents, the determination of the optimal dosage and combinations that can absorb a major part of the activities of many cancer centers, other aspects of cancer research in the aged deserve more attention. These include research designed to facilitate the early diagnosis of cancer and to determine the advisability and intensity of treatment of the aged individual with a particular type of cancer.

A human's probability of developing cancer increases over the next five years from one in 700 at age 25 to one in 14 at age 65. Nearly half of new cancers occur in the 10% of the 65 and over population. The exclusion of older persons from clinical trials has led to an inability to develop proper treatment for them. Decline in immune function with aging, increasing cancer incidence, and decline in lymphocyte function, are fertile fields for research as is the delay period in the development of various cancers after environmental exposures, that is, radiation cancer, skin cancers, asbestosis, etc.

Elias and Lesnick have shown that early symptoms of cancer are unusual in the aged and that they are most often nonspecific in nature, such as weight loss and anemia. In only 30% is pain a presenting symptom. The finding of a mass on routine examination of an asymptomatic patient is common. More typical symptoms such as vomiting, jaundice, cough, hemoptysis and hematemesis are present in only 1% to 7% of cases. Eleven percent of the cancers are unsuspected and found only at necropsy examination. The course of cancer in the aged is often of a slowly progressive nature as shown by an average duration of life of ten years from the onset of symptoms of breast cancer cases treated with hormones, mastectomy and radiotherapy. In treated colon and rectal cancer, survival was over six years (17).

These findings point out the need for better methods of early diagnosis. A hopeful lead was provided by the discovery of a tumor specific constituent of metastatic cancer of the human digestive system, which can be detected by the presence of a specific circulating antibody in the serum (18). Unfortunately, the serum level of this chorionic embryonic antigen (CEA) has been found to be nonspecific and often elevated in the aged, particularly among cigarette smokers.

There is also the need for research to determine the advisability of intensive forms of therapy in which life expectancy is limited. Norcross has shown that in mild cases of chronic lymphatic leukemia, intensive treatment may promote progressive disease activity and the onset of severe complications (19). Weiss, Cooper and Boucot (1969) have noted that the operative risk of surgery for bronchogenic cancer exceeds the five-year survival rate in men over seventy (20). Methods for determining the rate of growth of cancer will be helpful in evaluating the need for treatment. An example is the use of multiplane chest x-rays in the determination of the rate of growth of a metastatic nodule in the lungs. By extrapolation it can be hypothesized that, in some patients cancer cells were present at the time of original successful removal of an ostensibly nonmetastatic primary cancer.

This raises the need for research into the question of host resistance to cancer in the aged. The Clinical Center of the National Institutes of Health has been studying the sera of patients who have had spontaneous regression of tumors, prolonged survival following incomplete surgical excision of cancer and prolonged remissions following chemotherapy for cancer in a study of host resistance to cancer (21).

Routine and advanced pathologic techniques have shown that the solar effects on the aging skin account for the high incidence of skin cancer among the fair skinned aged. Comparison of the cheek and the buttock of a generation that did not have bikinis show marked degenerative changes on the routine examination while more advanced techniques show fewer cell divisions and precancerous changes.

There is now a vast field opening of therapeutic possibilities in senile dementia in which advanced biochemical techniques enable us to know that there is a marked deficiency of cat (choline acetyl transferase) enzyme in the brain of such individuals. In an analagous way to the therapy of Parkinsonism with L dopa, lecithin may provide an effective therapeutic method of treatment if the formidable barriers of FDA approval can be met in a reasonable period of years. Physostigmine blocks the enzyme which destroys acetyl choline. Other therapeutic drugs may be found.

The rationale for the better response of aged females to hormonal therapy has been found to be related to an increased number of estrogen receptors among the aged.

Modern research with photometric techniques for evaluating bone density has provided the basis for the knowledge that estrogens do increase bone growth after the menopause, that is, decreased osteoporosis while careful epidemiologic research has shown the other edge of the sword, the increase in endometrial cancer in proportion to dosage and duration of estrogen therapy.

What have been the results of our research efforts and improved care of the aged through improvements in finances, housing, nutrition, etc.? It is not generally realized that in addition to the well known increase in life expectancy at birth, there has been a recent marked decline in the mortality of the extreme aged, those 85 years of age and over.

Rosenwaike et al has shown that there has been a substantial real decline in mortality among those in this age group between 1966 and 1977. Data from Social Security files on Medicare and the National Center for Health Statistics reveal that there was a 20.4% decrease in the age-adjusted mortality rate for cardiovascular disease and a 30.6% decrease in that for cerebrovascular disease. The effect of these reductions in mortality was only mildly reduced by an increase in cancer deaths of 3%.

We may attribute much of this improvement in mortality to the applied effects of clinical research in determining risk factors such as hypertension and cigarette smoking, in developing improved methods of treatment such as intensive care units, in changing diets, activity, etc.

However it is obvious that, more important than increasing life expectancy and with it such diseases as senile dementia, clinical research must be directed to improving the quality of life in old age through treating and ameliorating the changes of aging and disease and in improving man's adjustment to man and the environment. There have been many successes but more remains to be accomplished.

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Workshop I *(Part b)* Summary: Applied Biomedical Research

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The topics discussed in this workshop included the following: the recognition that a cadre of outstanding clinical researchers in geriatric medicine must be developed; the ethical dilemmas and practical difficulties surrounding informed consent by the institutionalized elderly who might participate in clinical research; the lack of clinical trials of specific therapies such as vasodilators, antihypertensives, and anticoagulants in the octogenarian with intractable heart failure, systolic hypertension, and myocardial infarction, respectively.

Because at least one half of elderly people who reside in long term care institutions have some degree of chronic organic mental syndrome, usually senile dementia of the Alzheimer's type, the issue of obtaining informed consent becomes paramount if clinical research is going to be performed on these patients. Written consent from the legal guardian or the committee of the demented individual can only be obtained if the research will have a possible benefit to the subject. Inherent institutional and interpersonal pressures may also complicate the obtaining of informed consent from nondemented institutionalized elderly patients because of their dependence on caregivers for basic needs. The analogy between the situation of prisoners and that of institutionalized elderly people was made in that both groups could conceivably suffer the same kind of pressures from nonparticipation in research projects. Currently, research on prisoners can only be done if it has to do with the conditions of being a prisoner, that is, the state of incarceration is integrally related to the research. A comparable restriction on research on long term care patients would severely impair our understanding of many of the diseases that occur in old age. There is a need for studies to assess the attitudes of elderly people (and their guardians) who reside in both community and institutional settings, and of health care providers and administrators of institutions, so that we can understand any resistance to informed consent in these groups and hopefully modify it.

Dr. Reubin Andres, Chief, Clinical Physiology Branch, Gerontology Research Center, acknowledged the difficulties in doing clinical research in the elderly, but emphasized the scientific and personal challenges of expanding the body of knowledge that is geriatric medicine as well as clarifying the mechanisms of age changes. He emphasized that "research geriatric medicine," as well as the training of young investigators in the techniques to carry out biochemical research in the elderly, are high priorities of the National Institute on Aging. In addition to the Gerontologic Research Center of the National Institute on Aging, training sites for future researchers are developing within the established divisions of gerontology and/or geriatric medicine at academic medical centers throughout the country. Established researchers in the classic areas of medicine should also encourage young investigators with interests in aging research.

The group discussed the pros and cons of cross-sectional versus longitudinal research emphasizing the generational and secular biases and selective mortality of cross-sectional studies, and the difficulties of outdated tests and test instruments, the high cost, and investigator and subject losses of longitudinal studies. It was suggested that freezing sera at each examination in a longitudinal study would allow an investigator to perform newly devised tests (when they should be developed) thereby acquiring longitudinal data that could not have been found had the sera not been saved. The development of normative data such as the progressive decrease in glomerular filtration rate in senesence (as well as many other parameters of renal function) was felt to be important in understanding the processes of aging as distinct from disease.

One commonly encountered problem in the elderly is systolic hypertension (1). It is known that systolic hypertension has a greater effect on morbidity and mortality then does diastolic hypertension in the elderly, yet we do not know whether the treatment of systolic hypertension will decrease the incidence of cerebrovascular accidents, congestive heart failure, myocardial infarction or mortality (2). A controlled clinical trial on the treatment of systolic and/or diastolic hypertension should include patients over the age of seventy-five as well as a cohort of patients over the age of eighty-five. It is the cohort of patients over the age of eighty-five which is the most rapidly growing segment of people over the age of sixty-five. The Hypertension Detection and Follow-up Program, which analyzed the effect of rigorous control of diastolic blood pressure versus less rigorous control, included both male and female patients up to age seventy-four (3, 4). It was noted that three separate studies in progress, one by the National Institute on Aging, one by the European Working Party on high blood pressure in the elderly (5) and a multicentre study in British general practices (6) may have the answers to the treatment of systolic and diastolic hypertension in the elderly.

Risk factors for cardiovascular morbidity and mortality in old age are not clearly defined. For example, the measurement of obesity is complicated by changes in body composition that occur with increasing age. Because fat increases and lean body mass decreases in senesence, one can actually be losing weight while replacing lean muscle with fatty tissues, thereby becoming "fatter." Only longitudinal studies will help us determine the impact of obesity and only for the given cohort under study since dietary, work and exercise patterns, may influence future cohorts. The relationship between the various types of hyperlipoproteinemias and cardiovascular risk factors has not been determined in senesence. Specifically, the level of high density lipoprotein that correlates with decreased cardiovascular morbidity or the amount of alcohol that increases the level of high density lipoprotein has not been determined in senesence. Alcohol, however, can have negative effects in old age, particularly on the exercise tolerance test where older patients get earlier angina if given alcohol. Type A personality does not appear to be a significant risk factor in senesence.

The use of anticoagulation in the elderly, both prophylactically and therapeutically, has gone through various phases. Clinical experience tells us that bleeding complications may outweigh the benefits of anticoagulation in acute myocardial infarction. A recent study, however, done on fully ambulant and relatively healthy survivors of an acute transmural myocardial infarction, showed that mortality and occurrence of second infarctions actually decreased (7). Unfortunately this study is not applicable to very old people, i.e. seventy-five years of age and over, as well as those with complications such as malignancy, atrial fibrillation, or mental disorders.

The use of digoxin in the elderly patient was also raised and numerous studies were cited that show that digoxin can successfully be discontinued in a high percentage of community and institutionally residing elderly patients who are in normal sinus rhythm with compensated congestive heart failure (8, 9). Further studies are needed to analyze the pharmacodynamics, pharmacokinetics and effects of discontinuation of many other drugs that are commonly used in the elderly.

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Workshop II Case Management and Family Involvement

Marjorie Cantor, Helen Rehr, D.S.W., with Vivian Trotz, M.S.W.

Twenty professionals including social workers, nurses, physiotherapists and other nonmedical health care staff met in Workshop II to discuss case management with and without family involvement in regard to the frail elderly. Before narrowing down the case management concept, the definitions governing the frail elderly, and what social needs may exist, the group affirmed that the social supports required by the elderly are not so much related to age as they are to such factors as the extent of dependency, that is debility (impairment) and economic deprivation (low social economic class). While age is not the predeterminant for drawing on the formal system of community and professionally based services, studies show that those over 75 years of age tend to require such aid more than those under 75 years. As the elderly become frail and dependent, that is, less self-sustaining for whatever reason, the informal support system identified as family, relatives, friends and neighbors in a type of network is seen as playing different roles in assisting the individual. In addition to the informal system, we identify the formal and quasiformal support system as including a range of services provided within the community. These include homemakers, aides, home chore services, friendly visiting, visiting nurse, meals-on-wheels, senior centers, health related services, the social security system and others emanating out of social, health, educational and religious facilities, which are lodged in the private, voluntary or governmental systems.

In reviewing studies of the social needs of older people, it is clear that family and significant others are most active in the planning and in the delivery of their own social services. Most of the elderly are not dependent, and live and die with proximity to an informal support system. Family members are the primary caregivers, and relatives, friends and neighbors can be and are supportive as well. There was early affirmation that when one assesses the interaction between families with their elderly members, there is evidence that the elderly do as much for their children in rendering assistance as do adult children for their aging parents. In general, there is indication of reciprocity between the elderly and their children in giving comfort and help in a variety of ways. The social problems we identified quickly are those which exist for many independent elderly who do not have available to them social institutional assistance which could enhance their life patterns, and for the frail elderly who for whatever reasons are without adequate supports. The focus of this group is predicated on the philosophy that older people should remain in their communities with adequate provisions. Such provisions must allow for a social support system that permits socialization with a degree of regularity, crisis intervention as it is required, and for the tasks of daily living to be manageable without or with available assistance.

We agree that a definition of what all of us referred to as the "Social-Health Care Continuum" is in order, so that we can better deal with a discussion of needs and service projections. We offer that the continuum should be seen as "a system of need identification and service provision which guarantees that the health and social needs of an aging individual are met at levels commensurate with the degree of incapacity. This implies that needs will be addressed over an extended period of time with the appropriate type and intensity of intervention as determined by periodic reassessment of needs and capabilities, on the one hand, and available resources, on the other." We all agreed that for our purposes the conceptual framework of person-environment fit offered a means by which to assess the social-health status of an elderly individual. Person-environment fit refers to the degree of congruence between an individual's needs, capacities and aspirations and his environment's resources, demands and opportunities (Coulton, 1979).

There is considerable discussion on the extent of positive living arrangements most elderly have. The experience of the group members leads them to be impressed by the numbers of older people who remain active in their communities serving in volunteer and employed capacities, making contributions as volunteers in hospitals and other social agencies, working as baby sitters and in a range of other jobs. Their availability in crises and in family stress is attested to by indications of grandparents taking in children or grandchildren, offering support, love and other assistance as possible. For elder persons who are without families, there are resources cited such as one in Cooperstown, N.Y., where homes and apartments have been set up to support the independent lifestyle of single unattached persons, accompanied by social supports when need is evidenced. The group acknowledges that more of such resources are needed, to safeguard the continuance of elder persons in the community.

We turn then to the types of situations with which most social workers are familiar. There are those elderly who do not have what M. Cantor refers to as a "functional family". (M. H. Cantor: "The Informal Support System of the Familyless Elderly—Who Takes Over", paper presented at the Annual Meeting of the Gerontological Society, Dallas, Texas, 1978.) These are persons facing advancing age who may be widowed, separated from their adult children by distance or even emotional distress. While relatives such as siblings can and are helpful, they rarely can assume primary caretaking responsibilities. Studies suggest that perhaps one out of every five old people may be without any informal supports. Who can assume responsibility to assist these people? These familyless elderly welcome support from the formal support system to be found in the community. However, many agencies sponsoring programs for the elderly prefer and expect a family member to be available to them, so that responsibility can be assumed within the kin network. Thus, there are not many programs available to familyless elderly who are frail and may have considerable needs which are identified as dependent. Sometimes, these frail elderly may move in and out of a dependent-independent situation as a result of temporary crises, and need assistance to safeguard continuance in the community. Social workers do see such individuals when crisis strikes. They note their experiences with these elderly that as the crisis tends to subside, over time the strengths of these older people resurface, attesting to their ability to manage. Of course, there are those who may not be able to continue in the community and they will require specialized long term care.

We next begin to discuss the frail elderly with family support in which, for whatever reasons, the family has become exhausted or faces emotional strain from on-going caretaking responsibilities. When strains surface, they are not usually financial (although money availability can be problemmatic), but they are usually the result of an enforced, restricted personal social life. The impact of caring for a frail elderly person may impact the nuclear family in a range of ways. The problems may fall on a spouse who is with physical limitations and thus imposes supportive constraints. If it falls to an adult child, and invariably this is the female rather than the male child, then that individual may encounter a host of social deprivations in his/her own life situation, family interrelationships and, in particular, relationships with spouse and children. Experience tells us that these families who have been supportive need periodic respite from the demands. They do not want to be excluded from helping, but continuance can become unendurable without respite and support services. Working mothers have services caring for their children, why not such services for dependent elderly, for example, home aides.

Social workers in hospitals have observed that perhaps 10% of hospitalized patients (the elderly in particular) may call on 90% of the staff time. Most family units make their own discharge plans. Even the sick elderly are cared for by their families. Some social workers hold to the myth that the elderly are without family support. It is important for families to get recognition for their contributions. However, there are situations in which the crises have stretched the family's capacity to go on in the same way. These families need the assistance of the community social agencies. The formal and informal supports need to find ways to link with each other to reinforce the potential strengths of each. Families, and the elderly person need to be aware of the entitlements, services and resources available. Should these functions be components of case management?

What is case management? Does a need arise when crisis impedes the continuing contributions of the informal support system? Is case management a service that should be available to the familyless elderly person, in need of services if he or she is to remain in the community? Do we consider case management for the frail elderly determined by a set of definitions acceptable in social policy? Should case management be available to everyone from the age of 65 years and over, as we project their trajectory along a social-health care continuum? While case management for the elderly in a continuum of care projection is considered an ideal, none of us believes it is on the immediate horizon. There are even those who believe that 100% of case management services can be an artificial superimposed structure competing with existing programs which could make provision for needed overseeing services if they could get together on coordinating their tasks in the interest of the elderly person.

In any case, most of us agree there are situations which call for case management services. These are not limited to the familyless elderly who may become unable to continue self-care without help, but should include those families who are supportive and who encounter crises which stretch them beyond personal and social endurance.

Case management is seen as a service that requires assessment of need and, through a case manager coordinator, provides the connection between the formal and informal support systems. It becomes the mediating factor within the formal system on behalf of the informal system making linkages. Case management could be a permanent arrangement or an intermittent one. The process requires ongoing overseeing of the individual and/or family situation, with follow-up that includes periodic reassessment of the needs and services linkage. There will be situations in which the case manager function could be that of trainer to an informal support system member, teaching what is available in the way of services, and very importantly, teaching awareness as to when to call in an expert. The trainer would help the family member know that there is a back-up consultant who remains constant to the unit of need. In such events, the case manager continues to be a family member, within the nuclear network.

Case management, while it would serve to keep individuals in the community, need not be limited to those individuals alone. There are social workers who believe that case management services should be extended to those who enter long term care institutions. They see the function of determining the "rightness" of the placement in the contest of validity, suitability and appropriateness. Periodic case management services could continue to safeguard the individual's rights. Most of us agree that, at this time, given the political climate and the fiscal situation, it will be frailty and crisis that will govern the validity for case management. Dollars may be made available for such situations, but it is doubtful that monies would be offered to meet the ideal of case management services within the concept of a continuum of social-health care for the elderly.

The issues which followed dealt with who should carry the case management role, and under what auspices should they be. There is no question among us that case management is and should continue to be a basic responsibility of the informal support system—a family member, in particular. The principal caretakers of the elderly, including those who are frail, are usually a spouse and/or an adult female child. There are those who believe that the formal support services which currently exist should expand to include a formal case management program in conjunction with a family member. If no family member is available, and a need exists, then such service should be made available directly to the individual. We do not touch on the wide range of other case management possibilities such as legal, guardian, conservatorship, recognizing the complexities of these functions.

Who should carry case management? Again there are those who believe it should be carried by professionally trained persons under the auspices of accredited social agencies. Some believe a training program would suffice for less than professionals, but paraprofessionals carrying case management functions should also be under the auspices of an accredited and accountable service program.

Our discussion concludes with recognition by all that there is much to address in conceptualizing programs for the elderly in need. There is a primary need to come together on a sound national social policy which safeguards old people in a physical, social and psychologic environment of quality and is caring and responsive to their needs.

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WORKSHOP III
The Elderly and the Social Health Care Continuum

Susan Blumenfield, D.S.W., Barbara Morrison, D.S.W., Joyce Stroh, M.S.W., with Ruth Fizdale, M.S.W.

After a day and a half of lectures providing information on biopsychosocial dilemmas of the aging population, workshops were scheduled so that participants could come together to discuss some synthesis of the issues raised.

Workshop #3 was designed to study the elderly in relation to the Social Health Care Continuum. The charge to the group was to critically examine the concept of the social health care continuum and to discuss the possibility of operationalizing such a concept.

The workshop leaders provided a definition as a starting point for the discussion and provided an outline to guide the discussion toward addressing the following questions.

1) How can the needs of an aging individual be assessed? What variables are important to consider in assessing needs in relation to environmental supports?
2) How can resources and the existing service delivery system be assessed? What would the ideal social health care continuum look like?
3) Given the current state of health care and social service funding at the Federal, State and local levels, what are some of the deterrents to actualizing the ideal concept of the social health care continuum?
4) How can identified deterrents be addressed through advocacy, legislative mandate and/or changes in policy regarding health and social welfare services for the elderly?

There were 25 participants in this discussion. They included seven social workers, three doctors, two physicians' assistants, one gerontologist and seven "consumers."

Definition of the Social Health Care Continuum

The workshop began with a definition given by the leaders: "A Social Health Care Continuum for the elderly is a system of need identification and service provision that guarantees the health and social needs of an aging individual are met at levels commensurate with the degree of incapacity. This implies that needs will be addressed over an extended period of time with the appropriate type and intensity of intervention as determined by periodic reassessment of needs and capabilities on the one hand, and available resources, on the other." This definition was supplied within the context of the concept of "person-environment fit" as described by Coulton in 1979; the degree of congruence and fit between a person's needs, capacities and aspirations and the availability of resources and opportunity in and demands by the environment.

The group immediately posed the need to look at the definition without regard to an individual's socioeconomic status. They also brought in the necessity of fit for healthy as well as ill individuals and concurred that "well-being" was a goal, rather than just the absence of illness.

The notion of a social health continuum implied "holistic care" to most of the group, and implied all phases of well-being, not just those within the range of incapacities. Therefore "incapacity" and disability was stricken from the definition and replaced with "levels of capacity" which would include incapacity. There was the feeling that health maintenance and prevention of illness were legitimate areas to be included in a care continuum. Global issues of avoiding air and water pollution, providing adequate nutrition, even creating mechanisms to support family stability could thus be included in an expanded notion of a continuum.

Discussion of what social health care continuum could look like branched out into the notion of control. Who would be in charge of a continuum? How would access be controlled? Could any one person or discipline remain gate-keeper to a total system? These were questions with which the group struggled even before agreeing on how such a continuum would look. A major point of agreement within the group was that consumers needed to become more responsible for themselves and more responsible for participating in the development of any care model. Fostering self-help whenever it was realistically possible was encouraged.

There was much discussion around the role of professionals in a care continuum. All agreed that professionals with specific expertise were necessary participants in any system of care. However, the amount and structure of professional involvement was an area dividing the group. Many participants raised concerns regarding the involvement of particular professionals. There were several who felt that physicians were often inaccessible and that certainly the desire of many people to receive medical care in their own homes was not being met. Concerns were discussed regarding bureaucratic "red tape," binding needed social services and preventing people from obtaining important assistance. Not only were professionals faulted, but the lack of consumer involvement was decried.

What group to cover a care continuum was another question raised prior to designing such a concept. Many participants felt that crises occur from "cradle to grave" and that ways of dealing with these needed to be spelled out for everyone. Pre-natal care was suggested as a beginning of a given social health care continuum. Others believed that even speculation about such coverage was unrealistic in these times. Since our mandate was to deal with the elderly and since there might be some possibility of change using this population focused approach, we agreed to stick to the 65 and over group. Could a precrisis track be anticipated within the older person's life situation?

The latter approach was agreed upon by the majority of participants but several continued to be adamant that only by dealing with different needs at different phases of the life cycle would a real social health care continuum ever be possible.

Another voice of dissent was that of a participant who felt that care for people had always been crisis-oriented and that it was unrealistic to consider any change in this. Most other workshop members, however, were willing to speculate beyond the past and present and were adamant about the need for prevention oriented care, rather than only crisis management. An analogy to the Interstate Highway System was given in which bits and pieces of construction occurred in various places throughout the country. Eventually all these were hooked up to each other and travelers could move from one end to the other, or up and back in-between with smooth effectiveness. This analogy was used to describe how a social health care continuum ought to look. Rather than separate scattered services, there should be more effective linkages which would connect one to another, assure a person access from one to another when his/her needs changed, and clear away eligibility barriers which impeded use of needed services.

With this, the group began to work very hard to describe services that the elderly would need and to fit these into a kind of continuum. Permeating the entire range of services was the need for health education and the strongly felt value that old people themselves need to have a hand in assessing their own needs and designing their own services.

At the level in which people have the most capacity, socialization and role development opportunities seem to be paramount. When people have greatest decrements, medical care and maintenance are in order. Senior Centers, job or volunteer opportunities, etc. begin the service continuum. The primary care, acute care and ultimately forms of long term care complete the continuum. Under the rubric of Long Term Care came community support, home health care, day care and day hospitals and residential facilities. These elements seemed to provide the discrete sections which it was suggested could be tied together into a continuum.

Assessment of Need for Care

The group heatedly discussed assessment of need as a method of gaining access to the care continuum. The medical model of assessment and access as it was felt to exist today was criticized as providing "too little, too late" and "for the wrong reasons." Multidisciplinary input into assessment was agreed to as necessary, but how, when and where such assessment could be made was controversial.

After sketching in the broad components of a social health care continuum it was deemed essential that people could enter the system at any point. Access and assessment only on medical grounds and by physicians were viewed as something to change. Social needs as well need to be considered as basic to obtaining service. Participants agreed that using only medical documentation was counterproductive for many elderly people, as deficits in the social support network as well as functional limitations created problems for people that needed to be addressed. Several workshop participants brought up, time and time again, the importance of the elderly person being involved in assessing his own needs. It was stated that professionals seem to make needs assessments for people almost independent of the person's perceived needs and concerns. Such a method of assessment clearly leaves out the principal participant thereby missing the essential ingredient.

The suggestion of decentralizing the assessment process was made as well as using personnel analagous to the "barefoot doctor" in China as first-line caregivers and assessors of need. Tied to the notion of the use of new types of personnel was that of the continuing need for integration of services.

Speculation on how to devise ways to assess needs and resources did not progress within the group discussion. Problems with the present system needed to be aired.

The "Noncontinuum of Care" as it exists Today

There were many in the group with "battletales" of how the system has not been working, from which some common themes could be derived. Several participants gave vignettes of their own or client's experiences with the difficulty of obtaining needed care. They discussed problems in finding a particular service to address a particular need, for example, escort when needed, reliable housekeeping, transportation, etc. Problems of paying for various kinds of services were discussed, as were problems in creating more comprehensive packages of services by pulling in a variety of agencies.

A class-system of health care was cited as a major deterrent to a real continuum of care. Disparate services variously funded created unequal access and unequal quality. The group agreed that fragmentation of existing services with no overall system of coordination was a major problem. Yet, it was also agreed that tightly intertwined services could ultimately lead to lack of choice for people as well.

The need for public information and education was brought up time and again. Many workshop participants believed that the lack of public information and health education was a major factor in services not being delivered to the right people at the right time.

The consumer point of view was advanced. Some group members felt that we were all discussing the continuum of care from the providers' point of view. They wished to look more at consumer needs and brought in such needs as housing, transportation, food and medical care as essential to the social health of the elderly. There was much discussion around these basic needs and whether services to meet these needs should be included in a discussion of the "social health care continuum."

It was agreed that any social health care continuum must be multi-dimensional and must balance services available with identified needs.

Recommendations for Balancing the Needs of Older Individuals with Available Services and Resources

People in the group tried to think creatively regarding serving the elderly. Several suggestions were made. Using well elderly as a resource in caring for the sick was one such idea. Creating better transportation systems to enable the elderly to be more mobile was another. Creating more on-site medical care for people was a third. This involved the concept of sattelite clinics, more home care, etc.

One participant advanced the notion of more self-sufficient communities in which the elderly would continue to be producers not just consumers.

An overriding theme continued to be that of encouraging participation by the elderly in planning for themselves with major emphasis on involvement of those who would receive particular services being involved in the planning for these. Specific mention was made of the need to involve those not always included, such as the poor. While major concern was that of consumer participation, the need for professional expertise was acknowledged as important as well.

Summary: Areas of Agreement within the Workshop

1. All participants agreed that health care planning and provision should include all citizens of the country, and meet the needs of all individuals regardless of age, sex, race, religion, economic status, etc.

2. It was agreed that while proliferation of resources for health care creates fragmentation and overlap, it does provide a variety of points of entry for consumers who have some preconceptions of where they will get the help they desire or have prejudices against some specific modes of obtain-

ing help. Needed is some system of education and opportunity to discuss need with the promise of appropriate referral and follow-up.

3. It was agreed that assessment of need of the elderly individual should have the contribution of expertise of various professionals, but the consumer is the one who knows what enters into his own sound health care and maintenance, and the consumer should be heard.

4. It was agreed that data must be collected and analyzed to determine the real costs of providing sound health plans for people.

5. It was agreed that we need more data on the efficacy of program approaches before we either discard existing ones, or run to implement new ones.

6. It was agreed that service recipients, together with multidisciplinary providers would be in the best position to develop a real "social health care continuum."

7. It was also agreed that the workshop raised more questions than it answered, but that raising the issues was major step toward attempting change!

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Workshop IV
Advances and Services in Geriatrics for Health Care Administrators

Mitchell M. Waife, Neil Dworkin, with Joan Segall, M.B.A.

It was the consensus of the participants in this workshop that we are on the threshold of a technical revolution in geriatric care. The goal of biomedical research on aging, for example, is to prolong the useful and active lives of the elderly and to raise the quality of their lives.

There is a concern for cost of services for the elderly, not just due to pure price increases and costs due to increased services, but also for the cost-effectiveness of institutional care, home health care, and other service delivery modalities.

Statistics from the American Hospital Association indicate the importance of addressing public policy issues concerning long-term care. The data indicates that approximately 11.3% of today's population are elderly.

In the next 50 years, the total population is projected to grow by 40%. By contrast, the elderly population is expected to double to a total of 55 million, or 22% of the population. Since 1975, the most rapid growth in the elderly population has been in the age 85+ category. Those aged 65+ are admitted to hospitals three times more frequently than those individuals less than 65 years of age.

Many potential nursing home residents are occupying beds in community general hospitals. There is also an increased percentage of patients residing in acute care facilities with chronic illnesses who could be cared for under alternative community support service systems or other institutional arrangements. In general, there is a disinclination of physicians to find alternative types of care, and a corresponding disregard for evaluating and assessing the *total* needs of the elderly. The latter could result in premature institutionalization instead of, for example, home care treatment.

There is a need for an Assessment Tool which could be used nation-wide. This is to be distinguished from the New York State DMS-1 score as a tool, which does not take into account patients at risk or patients' ages. The resulting model should view the elderly as in need of a continuum of care, ranging, for example, from acute care to home care and other community support services. At present, there is very little coordination between hospital and community services.

Further, while acknowledging that there is a need for more precise and timely discharge planning, it is important to consider the effects of utilization review upon the elderly. They may be released from the hospital more quickly, but in a more morbid state, and the "mechanics" of utilization review may result in an inappropriate placement. (For example, placing the patient in the first available bed.)

There is an intolerance of death outside the institutional environment. Families need to become more involved in delivering the care to their elderly relatives. Concomitantly, there is a need to emphasize more human and social policies on the national, state, and local governmental levels.

There was a discussion of Dr. Robert Butler's concept of a "Teaching Nursing Home" and of medical direction and the quality of long-term care in general. Medical students should routinely be rotated through long-term care organizations in order to be exposed to the geriatric population, both sick and well. There is a need to examine the impact of the nursing shortage on long-term care, and the corresponding role that the nurse practitioner might play in the provision of service to the elderly.

The concept of the Day Hospital was discussed, using the English model as a focal point. In addition, a participant provided a general description of the provision of hospital services in England and pointed out that the acute care ward and geriatric ward exist side-by-side. All forms of care are covered under the National Health Service.

Many elderly are not in need of total health care, but rather more simple, less costly, forms of care. For example, a bipartisan group of senators, citing what they call the "alarming escalation" of medical costs for the elderly, has proposed a six-year experiment in care at home for the elderly and disabled as an alternative to expensive hospitals and nursing facilities. Studies suggest that as many as 25% or more of the 1.4 million people in nursing homes could live at home if they had adequate support. Many locally initiated programs of service delivery rely on grant funding, a problem for planning the continuum of care needed by the elderly.

The session ended on a negative note, with the conclusion that our health care delivery system is disjointed, that there is a lack of physician-leadership in geriatric medicine and, conversely, that nursing schools are more successful in teaching geriatrics than are medical schools, and that there is a lack of a central theme in service delivery to the elderly.

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Synthesis

Samuel K. Elster, M.D., Rose Dobrof, D.S.W., Helen Rehr, D.S.W.

DR. ELSTER: Rose Dobrof, Helen Rehr and I will try to put together what has happened in the last two days.

Dr. Dobrof is Professor of Social Work at the Brookdale Center on Aging at Hunter College. She has been at the forefront of advances in the social aspects of gerontology, and was very helpful in planning this program.

DR. DOBROF: The title of what we are to do in this time is synthesis. I am not going to go with the philosophical definition of synthesis, which is a rigorous definition. Instead, the job of the person synthesizing is "to put together." The best metaphor of these two days probably would be that it has been a mosaic with some gleaming pieces.

I think also, Dr. Elster was too kind about my role in this symposium. I really speak here from a sister institution, Hunter College. I am probably in the best position of the three of us to say to Sam and Helen that, as a veteran of four years, this has been the most spectacular of all of the four Brookdale Conferences. They get better every year, and this one is really a beauty. The published proceedings will bear witness to its success.

The two days represent both the accomplishments and our aspirations in the fields of geriatrics and gerontology. Repeatedly during these two days, we have demonstrated the gains made through interprofessional and interdisciplinary collaboration. Yet we have a long way to go.

One point seems most impressive to me. It was first made by Professor Ethel Shanas and the later by Dr. Manny Rodstein. Ethel talked about the extraordinary importance of developing assessment instruments which were really designed for older people and were not the modification of instruments used with younger cohorts. Manny emphasized the same point in the session he led. This kind of conversion of ideas and experiences, medical and nonmedical, is one of the glories of the geriatric field. Particularly evidenced today, was the extent to which there is recognition by all the professionals who spoke from the various fields—a clarity of recognition—of the absolute imperative for a comprehensive approach to the problems of older people. Good geriatric care is truly an interprofessional enterprise.

For example, it was a fascinating discussion of psychiatric problems of cardiac patients; to see the real recognition of the unity of the person, and the necessity for this kind of approach.

I would like to highlight something which requires our best thinking and our best efforts in the years ahead, part of the exchange among Dr. Eisdorfer, Elaine Brody, and Dr. Leslie Libow. The issue of triage and the differences of approach should not be papered over. I think it is a problem which has to be acknowledged and worked on. The differences presented that affect our planning and our thinking were the type of decisions which professionals must make to offer appropriate services to older people.

How do we account for the reality of limited resources and, at the same time, continue the struggle for more resources to be allocated for the care of the aged? We must do both at the same time. We cannot approach the problem sequentially. The hard decisions have to be made, they cannot be escaped from. Current resource allocation cannot be taken as a permanent given, the struggle for more resources must be waged simultaneously. This is one of the most important struggles that will be mounted in the ensuing year until the occasion of the Fifth Annual Brookdale Conference. I hope we will all return to discuss it in a better light next year. Thank you.

DR. ELSTER: I would now like to call on Dr. Rehr, Codirector of this conference.

DR. REHR: I am struck with Dr. Dobrof's remarks which, indeed, surfaced the linkage of the social and medical services in caring for the aging. Ms. Brody, Dr. Libow, and Dr. Eisdorfer highlighted the conflict while putting forth the need for an alliance.

By and large, when the physicians spoke during this conference, they talked invariably about patients who were in dependent states and predominantly frail. Dr. Eisdorfer developed sets of principles on dementia with regard to the mentally frail. It is possible that we may be living with a large number of misdiagnoses on the part of the medical community. Are we seeing true dementia, or are we seeing what might truly be reversible conditions?

Physicians, working with the aged face questions of assessment and how to deal with individuals and families. In both the medical and nonmedical arenas, it suggests that practitioners cannot accept at face value what they are told. Nonmedical staff must be prepared to speak up and make a contribution to the diagnostic process as to whether the conditions are reversible or not. We should not be trapped by each other's failings. We must deal with the assessment tools that are relevant to the patient's condition.

Dr. Andres pointed out that we are living with old tools and tests that reflect diagnoses which may no longer be applicable. It would be fascinating indeed if we were dealing with elderly who are not labelled diabetics anymore because the lab tests are misinterpreted. We should then be working with people who could live with less drugs, and without the label of a condition. Similarly, it would be so important to know that we have been miscalculating obesity and that studies suggest that we do better if we are ten to twenty percent over what had been considered the desirable weight.

Recent advances in the treatment of cataracts in the elderly as reported by Dr. Jaffe are astonishing. People who are now having a return of their vision, and quickly at that, admit the improvement to the quality of life. The future battle for the intraocular lens implant may be one for fiscal reasons rather than its value. Certainly, its availability is a critical finding.

There are many medical, clinical, and social environmental turn-around opportunities that professionals must keep abreast of. What is potentially and already available for the elderly? What can return people to a more optimal state than we have seen in the past? Ms. Brody makes the observation that the social and physical functioning of an individual are more critical in the care of the elderly than the disease per se.

It is true that the course of a disease is important, and warrants treatment. Yet, there is no question that disease and the individual's functioning are a mosaic to be put together. We know that disease does not necessarily predicate the physical functioning or social functioning levels of the elderly person, all factors should be related.

Finally, as Ms. Brody and Dr. Shanas emphasized, we simply cannot ignore the family as the principal provider of services to the elderly. They must be perceived as full partner in the long term social health care enterprise. To ignore the family, the basic support of most elderly today, is to avoid a major resource in the community.

There must be an appropriate mix of the informal and the formal support service systems. Case management for the most infirm and needy may be one mechanism. The informal and the formal systems will need to be coordinated so as to serve in the basic interest of the people who need them. Whether linkage is through coordination, case management, a monitored referral system, or the maintenance of centralized services systems, the issues of fragmentation and what is needed must be addressed directly.

The formal support system should complement the informal support system, not take over. Workers in the formal system often think they are the sole providers. It is simply not true. We who are in the business of social welfare must address social policy around the informal system as well as the formal. We must recognize the value of filial allegiance, that it does remain intact. However we cannot lose sight of the fact that the support system is essentially female oriented, not exclusively at the level of the adult child, but moves into the next generation at the granddaughter level. The support system is sustained very fully for grandparents, and questions that are asked are how to share in the care.

It would be presumptous to think that there are immediate resolutions on the horizon. But these conferences indicate there are so many who are preparing for the challenge of how to really begin to work and address the social and health problems of older people.

DR. ELSTER: I would like to add a few remarks. It is possible to have an interdisciplinary conference and hold the attention of people from many different areas because of a common goal. The social work and medical people have had an impact directly on the other. This meeting has given excellent examples of how research can be translated into clinical practice. Dr. Holland spoke of the specter of the serious nature of cancer. In the past twenty-five years, research, has enabled change of methods of treatment resulting in better clinical outcome for the individual patient.

Controlled clinical trials have contributed to the forward advancement of better health care. It is now possible to forecast in a woman with breast cancer on the basis of past experience and current clinical trials, the prognosis of the patient and to select the appropriate treatment for the individual patient. We can look forward to the day that a diagnosis is made, proper therapy can be administered to effect significant improvement in duration and quality of life.

Dr. Eisdorfer's remarks were most provocative. It is an interesting point that, in our four conferences, we have always come back to dementia, one of the most serious aspects of the aging process and one which still defies our proper management. Reversible dementias are being recognized more frequently avoiding a nihilistic approach.

Dr. Libow introduced the subject of ethics, a subject that pervades all our discussions of the elderly. It is addressed through legal institutions for the elderly, through many different community groups and promises to become an important part of medical school curriculum.

Dr. Austrian described the serious implications of pneumonia in the aged. On the basis of his work with the pnenmococcal vaccine, with proper utilization of this mode of prevention, pneumococcal pneumonia may be effectively irradicated in the future, just as proper vaccination has essentially eliminated polio except for a few sporadic cases.

Excuse the pun, but it was an eye opener to listen to Dr. Jaffe. I am often called upon by my patients to give cardiologic clearance for the cataract procedures that have to be done. Things have changed so vastly in that field. I can easily recall a patient who had to have a cataract extraction being confined to a hospital bed for ten days to two weeks. Often, the patient suffered from cardiac and pulmonary complications. Today, a cataract extraction is almost an ambulatory process. Thinking in terms of cost/gain ratio and allocated resources, this procedure, properly executed with good supervision, can save a great deal of money for the health care system and eliminate the now ophthalmologic complications for the patient.

Most importantly, in dealing with the elderly whose vision is impaired, the quality of life is so curtailed that often the criterion for treatment used by the ophthalmologist has been the patient's ability to read, watch television or function in daily activities. Improved quality of life is restored now through this fairly precise and simple operation.

Dr. DiGiacomo, whom we lost from Cardiology and gained in Psychiatry, gave us insight. At times, I am not sure I agree completely about the role of the emotions on the cardiac state or, conversely, the cardiac state on the emotions, but we do agree on the importance of treating both.

From Dr. Shanas and Ms. Brody, I learned the medical impacts on the social and vice versa. We all need to work together with the patient and the family to provide a better quality of life as we grow older.

Finally, there is a certain amount of very healthy tension that exists among health practitioners. We need to engender the team spirit, each playing his role. The ultimate goal is to help the patient.

I would like to thank our speakers once again for their outstanding participation and the audience for their attention. We invite you to return next year for the Fifth Annual Brookdale Conference on Geriatrics and Gerontology. Thank you.

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